CIRCULATORY SYSTEM DEVICES PANEL

July 28, 1997

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CASET Associates, Ltd.
10201 Lee Highway
Fairfax, Virginia 22030
(703) 352-0092

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P R O C E E D I N G S (9:30 a.m.)

Agenda Item: Call to Order - Julie A. Swain, M.D.

DR. SWAIN: I would like to call this meeting to order of the Circulatory System Devices Panel. Dr. Stuhlmuller will read the conflict of interest statements.

Agenda Item: Conflict of Interest Statement - John E. Stuhlmuller, M.D.

DR. STUHLMULLER: The following announcement addresses conflict of interest issues associated with this meeting and is made a part of the record, including the appearance of any impropriety. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employers' financial interests.

To determine if any conflict existed, the agency reviewed the submitted agenda and all financial interests reported by the committee participants. It was determined that no conflicts exist.

In the event that the discussions involve any of the filings or firms not already on the agenda but which an FDA participant has a financial interest, the participant

should exclude him or herself from such involvement and the exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose progress they may wish to comment upon.

Appointment to temporary voting status. For today's meeting, all consultants will be deputized and voting.

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter dated October 27, 1990, as amended April 20, 1995, I appoint the following people as voting members of the Circulatory System Devices Advisory Panel for this meeting on July 28, 1997.

Dr. Samuel W. Casscells, III; Dr. Manuel D. Cerqueria; Dr. L. Henry Edmunds, Jr.; Dr. Thomas B. Ferguson; Dr. Alfred F. Parisi; Dr. Julie A. Swain and Dr. Swain will also be functioning as acting chairperson for this meeting; Dr. Cynthia M. Tracy; Dr. George W. Vetrovec; Dr. Ronald M. Weintraub; Dr. Janet Wittes. For the record,

these people are special government employees and are consultants to this panel under the Medical Device and Advisory Committee. They have undergone the customary conflict of interest review and have reviewed the material to be considered for this meeting.

It is signed D. Jacobson and dated 7-28-97.

Additional appointment to temporary voting status. Pursuant to the authority granted under the Medical Devices Advisory Committee Charter and the Center for the Devices and Radiological Health, dated October 17, 1990, and as amended April 20, 1995, I appoint Robert M. Califf, M.D., as a voting member of the Circulatory System Devices Panel of July 28, 1997. For the record, Dr. Califf is a voting member of the Cardiovascular Drug Advisory Committee in the Center for Drug Evaluation and Research. He is a special government employee who has undergone the customary conflict of interest review and has reviewed the materials to be considered at this meeting.

It is signed Michael A. Freedman, M.D., Deputy Commissioner dated July 22, 1997.

An additional participant for this meeting is Dr.

Lawrence Friedman from the National Heart, Lung and Blood Institute at the National Institutes of Health. He is going to be participating in a panel discussion. He will be here this afternoon. He has also undergone the same conflict of interest as the members of the panel. He will not be a voting member but will participate as a discussant only.

Agenda Item: Old Business, New Business

DR. SWAIN: A couple of housekeeping things. We have a mandated break at 10:30 to 10:45 so you can plan accordingly and lunch will be at noon and is it noon to 1:00 or 2:00? Noon to 1:00. The other thing is we will be having some more chairs and be opening up the back of this room when the Boy Scouts leave so there will be a few more seats.

What I would like to do now is have the panel members and our FDA consultants introduce themselves. Why don't we go around the horn? Tom?

DR. CALLAHAN: My name is Tom Callahan. I am the director of cardiovascular, respiratory and neurology at FDA.

DR. TRACY: Cynthia Tracy and I am an academic

physician at Georgetown University.

DR. VETROVEC: George Vetrovec from the Medical College of Virginia, Virginia Commonwealth University in Richmond. I chair the Division of Cardiology.

DR. WITTES: I am Janet Wittes. I am a biostatistician from Statistics Collaborative in D.C.

DR. PARISI: I am Alfred Parisi. I am chief of cardiology at Brown University in Providence.

DR. CALIFF: Rob Califf from Duke University.

DR. STUHLMULLER: I am John Stuhlmuller. I am a cardiologist with FDA and executive secretary for the panel.

DR. SWAIN: Julie Swain, University of Kentucky, cardiovascular surgery.

DR. EDMUNDS: I am Hank Edmunds, professor of cardiac surgery at the University of Pennsylvania.

DR. CASSCELLS: Ward Casscells, chief of cardiology at the University of Texas in Houston and Herman Hospital.

DR. SETHI: Gulshan Sethi, surgeon, University of Arizona, Tucson.

DR. FERGUSON: Tom Ferguson, cardiac surgeon at

Washington University in St. Louis.

DR. CERQUEIRA: I am Manuel Cerqueira. I am director of nuclear cardiology at Georgetown University.

DR. WEINTRAUB: Ronald Weintraub. I am cardiac surgeon at the Beth Israel Deaconess Medical Center in Boston.

MR. JARVIS: Gary Jarvis, I am the industry representative to the panel.

DR. SWAIN: Thank you. Is there any old business? Yes, the two absences we have today is Dr. Gilliam, one of our panel members who suddenly couldn't make it this morning. And Dr. Gooray, our industry representative, consumer representative, excuse me. They have not been replaced. Is there any new business?

The first part of this is the open public hearing and that allows anyone who wishes to comment about any devices before this panel to comment. Are there any people who wish to speak regarding anything related to the FDA circulatory devices panel?

Dr. Stuhlmuller has two letters to incorporate.

DR. STUHLMULLER: To be included in the record are

two letters that were received by panel members. One dated letter from Dr. Thomas H. McConnell and a letter dated June 25, 1997, from Dr. Arthur Fields, state their opposition to the use of transmyocardial revascularization for the treatment of coronary artery disease. In addition, I am also entering follow-up letters written to FDA by Dr. McConnell and Dr. Fields. In his letter dated June 25, 1997, Dr. McConnell states that he has taken a short position and a financial interest opposite to the sponsor. Dr. Fields in his undated follow-up letter to FDA states that he has no financial interest in the sponsor or any competing laser companies.

DR. SWAIN: We are now ready to begin our committee discussion on the device under consideration this morning, PMA application P-95-0015, PLC Medical Systems Inc., heart laser CO-2 laser system. We will begin with a company presentation of 30 minutes and then go to the FDA reviewers and then the panel reviewers. I would like to ask the company representatives to state your name and financial conflict of interest considerations.

Agenda Item: Open Public Hearing - Company

Presentation

DR. LINHARES: My name is Steven Linhares. I am the vice president of R and D and clinical affairs at PLC Medical Systems and I have interest in the company.

DR. STUHLMULLER: Can you say what your interest is?

DR. LINHARES: Stock interest. And Dr. Xavier Lefebvre has his bachelor's degree from France and his Ph.D. in biochemistry from Georgia Tech and he is the director of clinical affairs and he will be giving our presentation this morning.

DR. LEFEBVRE: And I also have some interest in the company.

DR. STUHLMULLER: You just need to state what your interest is.

DR. LEFEBVRE: Some stock. Madame Chair, members of the panel, good morning. I will talk today about TMR using the heart laser. And more specifically about the U.S. experience during the clinical studies that took place between 1990 and 1997.

The proposed indication for use we are seeking

approval for is as follows. Transmyocardial revascularization with The Heart Laser CO2 Laser System is indicated for the treatment of patients refractory to medical therapy who suffer from chronic angina secondary to myocardial ischemia not treatable by direct coronary revascularization.

The data you are about to see will support this clam. It will show that TMR relieves angina, improves profusion and improves quality of life. Additionally, TMR has been shown to be assisted with the same modality as medical management and to have a lesser morbidity.

But let's look at the design of the system. The heart laser was designed to meet some important requirements. The first one is the system was designed to operate on the beating heart to minimize surgery trauma; however, when you operate on the beating heart, you incur the risks of arrythmia. Therefore, the system is synchronized to the ECG so that the laser is fired when the heart is electrically inactive. It is also very important to minimize tissue trauma and that such trauma is typically caused by either thermal damage or mechanical damage.

To minimize thermal damage, the heart laser uses a cardioxide laser because the energy of such laser is very well absorbed by tissue. Therefore, the energy is used to create the channel. It is not dissipated as heat within the surrounding myocardial.

Additionally, the system uses a high energy laser so that the channel, the transmural channels, can be created within a single pass. This results in more uniform channels and avoids the trauma associated with multiple passes. It is to me those requirements that the heart laser was designed as a high energy single synchronized carbon laser.

So how is the procedure done? After having accessed the heart through a left thoracotomy approach, the handpiece is placed on the heart, and the surgeon depresses the footswitch. The heart laser then synchronizes firing with the ECG, successful channel creation is confirmed using TEE and within minutes the epicardial surface of the channel closes.

So what happens after the TMR procedures? It is clear at this point the actual mechanism of TMR has not been fully understood; however, mechanisms advanced in peer

review journals as well as our own experience indicate that direct perfusion through the TMR channels or indirect perfusion through an angiogenesis growth affect may best explain the TMR mechanism.

Today we are going to talk about the 400 patients who were part of the U.S. clinical studies. The study was connected in three phases. Phase one was a pilot study which involved 15 patients at one site, Seton Medial Center. The object here of the study was to access the feasibility of TMR using the heart laser.

Following successful completion of this pilot study, a phase two, prospective multi-center patient controlled study was started at eight U.S. sites. The study involved 201 patients suffering from refractory angina who were not candidates for bypass or PTCA. The objectives of the study went to assess the safety and efficacy of TMR using the heart laser. The endpoint of the study were angina, perfusion, mortality as well as morbidity.

However, because of the design of the study it was not possible to obtain a proper controlled group to which the TMR resource could be compared. Therefore at the

request of the FDA, the company started the third phase, phase three, which was the prospective randomized study which was conducted at 12 U.S. sites. The study involved 198 patients, again class three or four angina and not candidates for bypass or PTCA. The patients were randomized to receive either TMR therapy or to be continued on medical management.

It must be noted that one of the limitations of the study was the fact that treatment assignment was not blinded since assignment of therapy was obvious to both patients and medical personnel. The objective of the study was to confirm the safety and efficacy findings of phase two using the following endpoint: perfusion, angina, quality of life, morbidity, as well as mortality. It must be noted that the crossover clause existed in the study which permitted medical management patients to receive TMR upon documented failure of medical treatment.

This crossover clause could be seen as a limitation because every crossover would result in the decrease in the size of the control group. However, the absence of such crossover clause would also have been a

limitation since without the incentive of crossover, it would have been very difficult to enroll patients in the study or once the patient had been enrolled in the study to keep them from dropping out of the control group.

These are the sites who participated in the studies. Eight sites participated in phase two; 12 sites in phase three. All of the 201 patients enrolled in phase two received TMR. OF the 198 patients enrolling in phase three, 97 received TMR and 101 were randomized to the control group.

The study populations were similar for both phase two and phase three and within phase three the characteristics were similar for the two randomized treatment groups. We you can see, all characteristics, demographics, chemical studies, medical history or risk factors are typical of what you see in cardiac surgery studies. It basically describes a group of high risk patients.

So let's first look at the results of TMR treatment. Between 30 and 36 laser channels were created. Of those, all but approximately five successfully reached

the left ventricle. The average energy used during the surgery was approximately 40 jus. Following the surgery, for the typical patient remained in ICU for two days and was discharged from the hospital seven to eight days after TMR.

The only complication not observed in bypass surgery was the accidental laser hit of the mitral valve apparatus. It occurred five times in one of the phase two patients, one of the phase three patients and three other patient groups. It has been noted that if you assume a number of 35 channels per procedures, the likelihood of hitting the mitral valve apparatus is 0.0001 percent. All of the other complications are typical of what is observed in repeat bypass surgery and the incidence was similar to the incidence observed in repeat bypass surgery shown on the right.

The TMR was designed to relieve angina so let's look at the angina results first. In this slide and in all the subsequent slides, the results for the phase two TMR group are shown in blue. In yellow are the phase three TMR group and in red is the control group for phase three.

This slide shows the percentage of patients with

severe class three or four angina at enrollment, three months, six months, and 12 months follow-up. The sample sizes for all three groups and all follow-ups are shown under the graph. As you can see, all patients were class three or four at enrollment. At all three, six and 12 month follow-up, slightly more than 20 percent of the TMR patients remain class three or four. This compares to the approximately 90 percent of the control patients. The difference between the two groups was statistically significant.

Therefore, it is clear from that slide that TMR relieves angina while medical management fails to do so.

If you look at the other extreme and concentrate on patients who did well and had class zero or one angina, you can see that obviously there were no such patients at enrollment and that all three, six and 12 months afterward approximately 50 percent of the TMR patients were suffering from minimal angina. This compares to the less than five percent of the control patients. Again, the difference between the two groups was statistically significant.

So we have now looked at those patients who did

well and those patients who did not do well but it may be more complete to look at the change in angina. The change, an increase or decrease of one angina class, is not always clinically significant; however, a decrease of two angina classes is always considered to be clinically significant. Therefore, as described in the clinical protocol, angina success was defined as a decrease of at least two angina classes at follow-up.

At all three, six and 12 months follow-up, between 65 and 75 percent of the TMR patients experienced a decrease of two angina classes. This compared to less than 10 percent of the control group, again the difference was statistically significant.

However, to insure that the improvement of angina was not due to an increase in cardioactive medication, nitrates, beta blockers and calcium channel blockers were monitored throughout the study. Among the patients, 11 of the control patients, 11 percent of the controlled patients experienced a medication decrease at follow-up among those patients who had a decrease of two or more angina classes. This relevant percent has to be compared to the 50 percent

of the TMR patients in phase two and 47 percent of the TMR patients in phase three who also experienced a medication decrease. Therefore, the medication profile of the two groups, TMR or control, seems to be different, but let's concentrate on the TMR group directly.

You can see that in phase two, 86 percent of the patients and in phase three 82 percent of the patients had either a medication decrease or no change in their cardioactive medications. Therefore, it is clear that the improvement observed in angina following TMR was not due to an increase in cardioactive medications.

We have also looked at the quality of life of patients in the study. The first of the two validated tests that we used was the short form 36 or SF-36 which is a generic measure of health status and captures the general, the overall quality of life of the patient. The test can be summarized in two indexes capturing the patient's perception of their quality of life which respect to their physical health and mental health. The test is scored between zero and 100, zero being the worst call. You can see than in both scores, TMR patients felt better following the surgery

while controlled patients did not significantly change.

The second test that we used was the Seattle Angina Questionnaire which specifically looks at the impact of angina pectoris on the quality of life of a patient. Again, the test is called between zero and 100, zero being the worst. The test has four key components and I will not go into the details but you can see that for all of the components, the scores went from a low value at baseline to an improvement in the TMR patient. The patient basically, the TMR patient felt that angina had less of an impact following surgery. In contrast, controlled patients did not believe that their quality of life was less impacted by angina at follow-up. All the difference between the to groups as statistically significant for all parameters and all follow-ups.

One of the primary endpoints of this study as myocardial perfusion. Myocardial perfusion studies provided a scientific and objective way of assisting the TMR efficacy. In phase three, we had a strict nuclear protocol which called for a thallium 201 SPECT Tomography studies to be conducted under rest and dipyridamole stress

conditions. The tests were to be done at study enrollment and at three, six and 12 months thereafter. All tests were analyzed by independent core laboratory which was blinded as to treatment assignment and timing of the studies.

The core laboratory analyzed the results using a 12 segment model for the left ventricular free wall and a 12 segment model for the interventricular septum. The results were then analyzed for the left ventricular free wall and the left heart, the left heart being composed by the left ventricular free wall and the septum. The analysis was conducted in a pair fashion with the follow-up results compared to the baseline findings and, of course, the results for the TMR group were compared to control.

This slide shows the perfusion results for phase two with the results for the left ventricular free wall being the solid green line and the result for the left heart being the dashed green line. You can see on the graph on the left the change in fixed defect. There was no statistically significant change in fixed defect at follow-up. This is very important because it is indicated that TMR was not associated with an increase in permanent myocardial

damage. That means TMR did not further injure the myocardial.

The graph on the right shows the number of reversible defects, and you can see that ischemia were used during the first six months of the study before leaving off thereafter. The change from baseline was statistically significant at six and 12 months for both left ventricular free wall and left heart. Therefore, the conclusion from the slides are that there was no significant change in fixed perfusion defects while there was a significant release in ischemia.

It must be noted that one of the limitations of phase two was that we did not have a set protocol for the nuclear studies. As a result, the attrition rate during the perfusion analysis process was somewhat high as you can see form the sample sizes in the figures. However, this lower sample size did not prevent us from reaching statistical significance in the endpoints.

This slide shows the profusion results in phase three for the left ventricular free wall. The graph on the left shows the change in fixed defect at follow-up for both

TMR group and control group. Again, there was no significant increase in the number of these defects which confirms the finding of phase two for the TMR group. This result also matches the low incidence of AMI observed during the study.

On the right you can see the changes in the number of reversible defects at follow-up and you can see that control patient wasn't, as far as ischemia was concerned, where the TMR patient improved. There as a statistically significant difference between the two treatment groups at follow-up. So this slide therefore shows that TMR relieves ischemia while perfusion wasn't in the control group.

One of the limitations of phase three was a result of the complicated analysis process required to analyze nuclear studies. It is a multi-step process which is very challenging. As a result, again, there was a somewhat high attrition rate in the nuclear studies; however, again, this maybe lower than desired sample size did not prevent us from reaching statistical significance in the desired endpoints.

This slide shows the results, the perfusion results in phase three for the left heart. Again, on the

left, you have the results for the fixed defect which confirms the findings of the left ventricular free wall. On the right you see the results for the reversible effect and you can see that ischemia wasn't in the control group while again it improved in TMR patients. Again, the difference was statistically significant between TMR group and control group.

Because of the attrition rate observed in the study, the number of 12 month scans viable at 12 months was not sufficient to permit a stand-alone analysis; however, it is possible to combine those 12 month studies with the available six and three month profusion data to form a last follow-up type of analysis.

This analysis is shown there for phase two and phase three. This analysis also permits to compare the phase two findings to the phase three findings for the TMR group and you can see that in both left ventricular free wall and left heart the results for phase two and phase three TMR were similar. However, when comparing the result between TMR groups and control group there was a statistically significant difference in both left

ventricular free wall and left heart, confirming that TMR significantly improved perfusion while controlled patient continued to worsen.

So we have now shown that TMR relieves angina and also that TMR relieves ischemia. That is why, to see if there was a match between the two findings. The question that needs to be answered is whether those patients who were clinically successful from an angina standpoint, i.e., a decrease of two angina classes also experienced a change in perfusion. Such patients would be in region C. They would have a reduction of greater than two angina classes and an improvement in SPECT changes.

On the opposite, it is also important to look at those patients who failed to experience a clinically significant relief of angina. Where these patients, did this patient experience a lack of improvement in perfusion changes. This patient would then be in region B. By adding together the number of patients in region C and region B, you can obtain the total number of accurate predictions, divided by the total number of scans available and you can obtain the agreement between angina outcome and perfusion

outcome. This agreement was 62 percent in phase two, 75 percent at six months in phase two and 66 percent at 12 months in phase two. In phase three, the agreement was 68 percent at both three and six months.

The average agreement between angina outcome was and perfusion changes was 67 percent in phase two and 68 percent in phase three. They were there for a good agreement between the perfusion changes and the angina outcome.

So we have now looked at the efficacy endpoints. Let's look at the safety endpoints.

This slide shows the mortality observed during the study. It must be noted that this slide includes all death, study-related or not study-related. For example, there were some TMR patients who died in a house fire. They are included in this analysis. You can see that the mortality observed in all three groups, phase two TMR, phase three TMR as well as phase three control for those patients who remained on medical management throughout the study was similar. In fact, the one year survival was 83 percent for the TMR group versus 82 percent for the control group.

The key mobility event to monitor is the incidence of unstable angina. This such evidence are very painful and dangerous for the patients. You can see that one year into the study, 95 percent of the TMR patients did not have such event; however, in the control group slightly over 30 percent of the control patients remained free of unstable angina event. The difference between the two groups was statistically significant.

Another key event is the incidence of acute myocardial ischemia. You can see that after one year into the study, 95 percent of the TMR patients remained free of acute myocardial ischemia. That number must be compared to the 82 percent seen in control patients. There was a statistically significant difference in with respect to the incidence of AMI between the TMR group and the control group.

However, it may be more complete to look at the combined endpoint which looks at the freedom from death, AMI or unstable angina. At the end of the one year study, slightly less than 80 percent of the TMR patients remained free of any of those three events. These numbers must be

compared to the 25 percent of the control patients who remained free of death, AMI or unstable angina at the end of this study. Needless to say, this difference was statistically significant.

And finally this slide may be the best representation of the clinical picture seen during the study. This slide shows the freedom from death, AMI, unstable angina or recurrence of class four angina. The data is shown for both phase two and phase three, TMR group as well as for the phase three control group. You can see that at the end of the one year study, 60 percent of the TMR, more than 60 percent of the TMR patients will remain free of any of those four events. That compares to 10 percent among the control group. Again, the difference was clinically as well as statistically significant.

So what are the conclusions that can be drawn from this study? First, TMR using the heart laser significantly improved myocardial perfusion while medical management did not. More specifically, the reversible myocardial damage did not significantly change for either a TMR patient nor control patient. However, ischemia significantly decreased

in TMR patient while it did not so in control patient. The improvement observed in perfusion and ischemia relief led to the improvement observed in angina pectoris and TMR using the hot laser significantly improved angina pectoris while medical management did not. More specifically, between 65 percent and 75 percent of the TMR patients versus less than 10 percent of the control patients experienced a decrease of at least two angina classes.

This improvement or lack of improvement in angina pectoris was reflected in the quality of life findings and TMR using the heart laser was found to significantly improve quality of life while medical management did not. In fact, when looking at the average quality of life index, it increase 116 percent for the TMR patient while it basically remained unchanged at 13 percent for the control patients.

Now looking at the safety endpoint, TMR using the heart laser was associated with similar mortality as medical management. In fact, the one year survival was 83 percent for the TMR patient versus 82 percent for the control patient who only received medical therapy.

And finally, TMR using the heart laser carbon

dioxide laser system was associated with less morbidity than medical management. In fact, 29 percent of the TMR patients versus 90 percent of the control patients experienced either death, AMI, unstable angina or the recurrence of class four angina. Thank you very much.

We will have a panel of investigators ready to answer any questions the panel may have after FDA's presentation.

DR. SWAIN: Thank you for your timely presentation. The next presentation will be by the FDA reviewer, Judy Danielson.

Agenda Item: Open Public Hearing - Panel Reviewers

MS. DANIELSON: Good morning. My name is Judy Danielson. I am the primary reviewer for the PMA application under consideration this morning. I would like to begin by introducing the other FDA staff who participated in the review of this application. Medical Officers Paul Chandeyson and Steven Kurtzman, John Dawson, a biostatistician, engineers computers and Brad Aster, Tara Ryan, branch chief of the interventional cardiology devices

group and Dan Spyker, deputy director of the division of cardiology, respiratory enterology devices.

What we would like to do in our presentation is provide an overview of the clinical data and present questions for the panel to consider during the proceedings. Steven Kurtzman will begin with an overview of angina and adverse event data.

DR. KURTZMAN: Good morning. I will be presenting what the FDA considers to be key results in angina and adverse event data obtained in the PLC Transmyocardial clinical investigation as well as important points to consider in evaluating the data.

As already noted, the PLC clinical investigation was conducted in three phases. Phases one and two were non-randomized studies in which all patients underwent TMR. In the phase three study, patients were randomized to TMR versus medical management. In this presentation, I will only discuss phases two and three.

There was a high percentage of crossovers from medical management to TMR in phase three. Consequently, the phase three control patients were analyzed in three ways.

The first method of analysis was the intent to treat analysis where all available follow-up data were analyzed regardless of cross-over status. The second method of analysis was the control analysis where only follow-up data until the cross-over were analyzed. The third method of analysis was the control, non-cross-over analysis where only control patients who did not cross over were analyzed.

This slide summarizes the phase two an three angina treatment success data. Angina treatment success was defined as an improvement of at least two classes with a slightly modified Canadian cardiovascular society angina classification system. The percentages of patients experiencing angina treatment success at all follow-up dates were highest in the phase three unstable angina TMR group.

The next highest percentage of angina treatment success were in the phase two TMR group, followed by angina treatment success in the phase three randomized TMR group. Treatment successes in the three phase three groups was significantly less statistically than treatment success in phase three randomized TMR group.

Angina treatment successes experienced by a

majority of TMR patients may be partly due to the placebo effect for three reasons. First, the correlation of objective improvement in thallium perfusion with subjective improvement in angina is not very strong. Second, the few well done published animal and human autopsy studies have conclusively shown myocardial channels created by TMR laser close after approximately one and a half to two and a half months suggesting that any long term improvement in angina is not due to improvement in perfusion resulting from myocardial channels.

Third, several published studies indicate that the placebo effect can last a year or more.

This slide summarized the phase two and three mortality data. Thirty-day, long term and overall mortality were evaluated. Looking at overall mortality in the right hand column, it can be seen that overall mortality was highest in phase three unstable angina TMR group with 31 percent of the patients enrolled in this group dying.

Overall mortality ranged from 15 to 19 percent with the phase two TMR group. The phase three intent to treat control group and the phase three randomized TMR

group. Overall mortality was lowest in the phase three control non-cross-over group, being 13 percent in this group. Kaplan Meyer analyses showed no statistically significant differences in overall survival among the phase three randomized TMR group, the phase three intent to treat control group and the phase three controlled non-cross-over group.

This slide summarizes the causes of death in phases two and three. The most frequent causes of death were myocardial infarction or suspected myocardial infarction, heart failure, respiratory failure, ventricular fibrillation, coronary artery disease, and arrythmia or apparent arrythmia. These causes of death are not unexpected in the patient population study.

In the phase two TMR group, the cause of death was unknown or unexplained in a relatively high percentage who died after hospital discharge.

This slide summarizes non-fatal adverse events in phases two and three. The most frequent non-fatal adverse events were life threatening arrythmia, unstable angina, congestive heart failure, cerebral vascular accident, and

acute myocardial infarction.

There are three important points to consider when evaluating the data from this clinical investigation. The first point is that the clinical investigation was not designed to definitively allow impossibility that TMR works partly by the placebo effect. The second point is that the angina and thallium perfusion data are not available for all patients enrolled in phase two and three studies. These studies overall angina follow-up compliance range from 72 percent to 90 percent and thallium perfusion data were analyzed for only 32 percent to 44 percent of the patients.

The third point is that there was a high percentage of cross-overs from medical management to TMR in phase three. Thank you.

The next presenter is Dr. Paul Chandeysson who will discuss the myocardial perfusion data.

DR. CHANDEYSSON: Good morning. During the next five minutes, I would like to review the myocardial perfusion imaging data. These data have already been presented to you on a statistical basis. The data were described in terms of groups of patients. I plan to review

the data on the basis of individual patients.

In order to do this in a reasonable length of time, I have plotted the data for individual patients in cartesian coordinates.

This slide shows the coordinate system I used. The change in the CCS angina class is plotted on the vertical axis and the change in the number of ischemic segments is plotted on the horizontal axis. Each patient who had a baseline and follow-up CCS angina class report and a baseline and follow-up myocardial perfusion scan reported will be plotted using the patient number because a decrease in the CCS angina class represents improvement in symptoms and a decrease in the number of ischemic segments represents improvement in perfusion.

Patients who improved both in symptoms and perfusion will be plotted in the lower left quadrant. I plan to show you seven plots of data, three for phase two at three, six and 12 months, and four for phase three at three and six months for the TMR patients and three and six months for the control patients.

In this way, you can see the data, and this may

help you form an opinion as to what they mean.

This plot is for phase two at three month follow-up. The four digit numbers on there are the individual patient numbers. There are 52 patients plotted, 28 of them are in the left lower quadrant. There were 201 patients in phase two, all of whom were treated with TMR and, incidentally, these data are taken from the individual patient line listed. This plotter for phase two and six months follow-up. Data from 44 patients were available to be plotted, 31 are in the left lower quadrant.

This plot is for phase two at 12-month follow-up. Data from 38 patient are plotted; 24 are in the left lower quadrant. This plot is for the phase three TMR patients at three month follow-up; data for 37 patients are plotted; 20 are in the left lower quadrant and this plot is for the phase three TMR patients at six month follow-up. Data for 32 patients are plotted; 16 in the left lower quadrant.

And now for a change of pace, this is the phase three control data at three month follow-up. Data for 26 patients was available; only two are in the left lower quadrant. You see, we had to enlarge the zero-zero block in

order to get all the patient numbers in. This plot is for the phase three control patients at six months. Data for 21 patients was available to be plotted; only one is in the left lower quadrant.

The points to consider in evaluating these data include one, the myocardial perfusion imaging data are sparse; only 32 percent of the patients in phase two and 44 percent of the patients in phase three contributed usable myocardial perfusion data. However, there is no evidence that the patients who contributed myocardial perfusion data are not representative of all the patients.

Two, the correlation between the perfusion data and the angina data is weak. The amount of scatter in the data is evident on these plots.

Three, the method of scoring the number of ischemic segment has not been validated; however, the same method was used to score the TMR patients and the control patients and the results for the control patients are consistent with the lack of improvement that was expected. This provides some validation of the scoring method.

Thank you for your attention. Now Judy Danielson

will present some questions for consideration by the panel.

MS. DANIELSON: The first set of questions relate to the labelling of the laser system. Currently the heart laser CO2 laser system is indicated from the treatment of patients with chronic angina, Canadian cardiovascular society class three or four, secondary to myocardial ischemia or coronary disease which cannot be treated with other types of conventional or direct coronary revascularization and who are refractory to medical treatment.

Do these indications for use adequately define the appropriate patient population? Which, if any of the alternatives in bracketed phases should be included in the indications for use?

Question number three, a total of 52 patients entered the unstable angina arm of the phase three study. Are the data form this study adequate to include unstable angina as an indication for use? Is the definition of unstable angina used in the study, that is, failure of three attempts to wean from IV anti-anginal drugs in seven days appropriate?

Currently the heart laser CO-2 laser system is contraindicated for use in patients where the ischemia is limited to the ventricular septum and/or right ventricular wall. Is the proposed contraindication as stated appropriate? Are there any additional contraindications for the use of this device?

Question number five. The mechanism whereby TMR relieves angina is not known. Theories include increased profusion of myocardia via the laser channels, increates collateralization via angiogenesis, symptom reduction resulting from disruption of pain fiber function and possible contribution of the placebo effect. These possible mechanisms of action are listed in section 12.3 of the labelling. Does this adequately summarize the current state of knowledge?

Question number six. Phase two perioperative mortality was 11 percent in the first half of the study and seven percent in the second half. This difference could represent a potential learning effect. Is the proposed Operator Training Program in section 12.6 of the labelling adequate? If not, how should it be modified?

Question number seven. Should the use of transesophageal echocardiograhy to verify successful creation of the laser channels be recommended for the clinical use of TMR?

And question eight, have you any other suggestions for the labeling?

In addition, FDA has some questions regarding patient follow-up. First, should additional long term follow-up data be collected on the TMR-treated patients? If so, what type of data should be collected and for how long? And secondly, are there any other issues of safety or effectiveness not adequately covered in the labeling which need to be addressed in further investigations before or after device approval?

Time permitting, FDA would also like the panel to comment on a few questions regarding appropriate trial design for TMI design studies. We will wait until your discussion of this PMA is complete before posing these questions.

This concludes FDA's presentation. Thank you for your attention.

DR. SWAIN: Let's have a break for 15 minutes and we will reconvene at let's say 10:45, 20 minute break.

(Brief recess)

DR. SWAIN: Let's reconvene the panel. What I would like to do first is ask the PLC representative to introduce their clinical experts and their company members that are available for questions from the panel members and to include the financial conflict of interest of each person who is going to speak.

DR. LEFEBVRE: The first advisory is Bob Rudko, Dr. Rudko is scientific chairman for PLC.

DR. SWAIN: And he owns stock in the company. We have got to have this on record so we will repeat it.

DR. LEFEBVRE: The next investigator is Dr. Larry Cohn from Brigham & Women's Hospital.

DR. COHN: No stock, no options.

DR. LEFEBVRE: No stock, no options.

DR. SWAIN: No stock, no options. I assume paid for transportation here.

DR. COHN: Yes.

DR. LEFEBVRE: The next investigator is Dr. Keith

Horvath from Northwestern University.

DR. HORVATH: No stock, no options and paid for transportation.

DR. SWAIN: Paid for transportation. No stock, no options.

DR. LEFEBVRE: The next investigator is Dr. Howard Frazier from Texas Institute.

DR. FRAZIER: No stock, options. Paid for transportation.

DR. SWAIN: Same for Dr. Frazier.

DR. LEFEBVRE: The next is Dr. Phil Lavin, statistician.

DR. LAVIN: No stock, no options, paid consultant.

DR. SWAIN: Paid consultant.

DR. LEFEBVRE: Next is Dr. Robert March from Rush Presbyterian in Chicago.

DR. MARCH: No stock, no options. Transportation paid for.

DR. SWAIN: Transportation for Dr. March.

DR. LEFEBVRE: Next is Dr. Finn Mannting from the Brigham and Women's Hospital, nuclear radiology.

DR. MANNTING: No stocks, no options. Paid consultant.

DR. SWAIN: Paid consultant.

DR. LEFEBVRE: Then on the second row you have Dr. Steven Boyce from Washington Hospital here in D.C.

DR. BOYCE: No stock, no options. No paid travel.

DR. SWAIN: No financial interest, Dr. Boyce.

DR. LEFEBVRE: Then Dr. Allan Lansing from Columbia Audubon in Louisville.

DR. LANSING: I have stock, paid for transportation.

DR. SWAIN: You have stock and paid for transportation for Dr. Lansing.

DR. LEFEBVRE: Then is Dr. Crew from Seton Medical Center in California.

DR. CREW: No stock. I have options and paid transportation.

DR. SWAIN: Okay, for Dr. Crew it is options, stock options and paid for transportation. Okay, thank you very much. So what we are going to do for the next several hours and we will have our break somewhere around 12:00,

12:30 for lunch is to ask our panel, they can ask questions of anybody from the company, their consultants or the FDA. What we usually like to do, since there are several new panel members for this meeting, is our two primary reviewers, Dr. Califf and Dr. Edmunds and we would like them to ask about 15 to 20 minutes' worth of questions. We will start with Dr. Califf and Dr. Edmunds and then we will go around the panel for about 10 minutes apiece and then we will go back and keep doing laps around until everybody has asked every question that they wish to ask.

So Dr. Califf.

DR. CALIFF: Thanks. As usual, I have about four hours worth of questions so I will try to hold it to 15 or 20 minutes and get it on the way back around.

This obviously is a really important hearing because the numbers of patients with this problem of refractory angina are growing exponentially around the world and so I think it is going to be an interesting discussion. My questions related to the presentation I think fall into four categories and I will just name categories and then ask questions.

The first is how to deal with so much missing data. I don't think I have ever seen a clinical trial presented where the primary endpoint had more than half the data missing so I am going to need some guidance and help from the FDA and the panel and the sponsor about how the missing data is handled, why it is missing, different ways of accounting for the missing data.

Second is a whole host of statistical issues oriented around how to interpret P values that have been quoted or presented, both in the briefing book and the discussion today.

The third has to do with assessment of angina, trying to understand bias or potential for bias and get a better understanding of how the assessments were actually done for the key secondary point.

And then the last is the assessment of morbidity which, I have a number of questions related to how it was assessed and what was done in terms of the analyses. So the first, and I would ask either the FDA or the sponsor, maybe hear form both about it is very hard to tell either from the material that we got, it is hard to actually trace all the

patients. Let me just say that for my questions, I don't care about phase two. That is all nice work that shows that there is a tenable hypothesis that the treatment works. What I am really concerned about is the phase three trial where we have a randomized control group.

Is it possible to take all the patients randomized in each group and to show first of all why patients, what happened to each patient and secondly for those who did not undergo the primary or the key secondary assessment, why that was not done?

DR. SWAIN: AS you answer your question, please state your name for our audio record.

DR. LINHARES: I am going to act as sort of a moderator on our end. My name, again, is Dr. Stephen Linhares. Dr. Lefebvre will go through the process of how we had to eliminate or explain why we had to eliminate some of the angina scoring and Dr. Phil Lavin is a statistician and he will explain the statistical significance.

DR. LEFEBVRE: Could you please put overhead number 25 of slide back up, number 23.

DR. SWAIN: Let me remind you, not that it is

appropriate to this that you cannot present any data that has not been submitted in the panel package.

DR. LEFEBVRE: All the data is either in the panel package or in the PMA. This is good.

You are correct that there was a high attrition rate in the primary endpoint of phase three. The reason behind it was it, the analysis of the studies were done using a multi-step analysis process and I will go in detail. The first step was, of course, that the patient had to be eligible for the test at both baseline which is obvious and follow-up. If the patient, for some reason, died, had an additional procedure or was not yet eligible for follow-up, that means we would lose the patient at both baseline and follow-up.

The next step that was involved was that the test had to be scheduled for protocol and the patient for that had to be able to undergo a stress test. If the patient had, let's say, unstable angina event at the time of follow-up, that patient could clinically not undergo the test. Again, a patient lost by follow-up.

The next step, step number three, was that the

test had to be completed by protocol. Again, that meant that the patient did not have a clinical event during this test which involves tracing. Of course, there were some cases where the protocol was not done and the next, I will show after that overhead another overhead which will describe where the patient, where the actual losses took place.

Once the test had been completed by protocol, the test data had to be downloaded onto a disk and shipped to PLC and then to the core lab. If anything happened to that disk in the process, that data could damage and so on, we could eventually lose the information because hospitals typically purge the memories of their computer system n a regular basis so if the disk was damaged, we could go back and get the data re-downloaded but often that was not the case so again some reason for losing patient data right there.

Finally, the test had to be in step six, the test had to be reconstructed by the core lab and that implied that there was no technical problem with the data, either from the way the data had been downloaded to disk or from

just looking at the patient. If the patient moved during the study, or if for some reason the camera was not centered adequately, those tests were not useable. Again, more reasons to lose the test and finally, when the tests were analyzed by, were read by the core lab, the tests were eliminated when there was no baseline ischemia.

So these are the different steps that were involved in the process, and as you will see in the next overhead, we lost a few patients that showed those steps. What that chart chose, it is also an independent package as well as in the PMA but --

DR. CALIFF: It is on page 94. You might, as you are going through, just might tell them what page it is on.

DR. LEFEBVRE: It is on page 94 of the final package. What we have done in that chart is tried to document where the losses occurred. First you can see going down from the top that we were able to characterize 86 percent of the studies. That means that really there were very few patients that we did not know what happened to them. Of those studies that were not useable, you can then divide and look at them as being preventable losses, losses

that the company could have potentially worked and tried to minimize but there was at the same time non-preventable losses which were independent or out of control from the company and also as a result of the paired design of the analysis, they were all the matching losses and you can see that non-preventable as well as matching losses would present 66 percent, two-thirds of the studies were lost for reasons that were totally out of control of PRC and I can list them.

In terms of non-preventable there were 19 percent of the losses related to death of the patient, 12 percent the patient had additional procedures, 41 percent of the patients crossed over, 12 percent there were some technical problems with respect to the tests and in 17 percent there was no baseline ischemia.

Was that answer the reason why we had 42 percent rate of analysis.

DR. CALIFF: I think I will get to some of what you call non-preventable losses to try to understand better why they were non-preventable but the part that baffled me maybe even more than the thallium studies was the angina

status which I would have thought would have been 100 percent ascertainment and it seems to be well short of that.

DR. LEFEBVRE: The data is shown on the panel packet on 63 or the TMR versus intent to treat group it is shown on page 71 for TMR versus control it is shown on page 79 for TMR versus control, no crossover. What you can see is that in all three analyses the compliance was 75 percent. This is due to the fact that some of the tests did not reach the company by the time we had closed the data base for analysis.

DR. CALIFF: I mean, you have data, at three months you have 8 out of 84 in the TMR group and 13 out of 84 in the intent to treat control group without an assessment of angina status. I mean, surely everybody had to reach three months at follow-up.

DR. LEFEBVRE: In the intent to treat that also included some patients post-crossover but this is the monitoring of the study is an ongoing process and when we closed the data base of the analysis, we used all the data that was in-house at the time.

DR. CALIFF: Since you have brought up closing the

data base, I would like to skip then to the question of how did you decide when to close the data base and how many times did you look at the results as the study was ongoing? How were the results monitored?

DR. LEFEBVRE: We updated, we submitted the PMA which was filed December 2 of 1996 and we updated the data at three months after filing of the PMA submission. That is how we came up with the data.

DR. CALIFF: So there was not a statistical rule or any data safety monitoring committee or any sort of external group that was evaluating data. You were looking at it yourself.

DR. LEFEBVRE: There was, we had a data safety meeting monitoring board which looked at the adverse events and that committee did not act in telling us of analyzing the data that they saw such data.

DR. CALIFF: So from what you are telling me so far, at least with regard to angina, you jut didn't get the data on 21 out of even at three months, on 21 out of 200 patients, 8 in the TMR group and 13 in the intent to treat group.

DR. LEFEBVRE: Correct. We don't have it yet.

DR. CALIFF: I need some help both from, maybe I could also ask Janet, Dr. Wittes, to comment on this. We deal with this problem in clinical trials all the time but usually not at this magnitude. One statement that I would make is perfusion imaging data as a primary endpoint when the goal of the treatment is to improve the health status. It seems like a treacherous step to take anyway but even assuming either perfusion data or angina status, how do you make statistical inferences when you are missing over half the data?

DR. LEFEBVRE: Dr. Lavin will respond to that question. Could you repeat your question?

DR. CALIFF: The question is what is the basis for making a statistical inference when over half the patients don't have the endpoint measured? Do you just pretend like they never existed or how can you do it?

DR. LAVIN: My name is Philip Lavin. I am with Boston Biostatistics and we rigorously pursued the characteristics of the patients who were in the SPECT analyses versus those who were not. I would like to draw

your attention to page 95 in the package that was sent to the panel. That is for the display of the phase three characteristics of the 92 patients with SPECT data versus the 116 who did not have the SPECT data. Terri, do you have that overhead?

Now, you can see here generally there is very good concordance between the group in terms of baseline characteristics of those who had the SPECT evaluations performed versus those who didn't have any SPECT as yet evaluated. In almost all categories you see comparability. I think as you look across the board, there is only smoking I believe is the only one where it was slightly higher for the SPECT, for the patients without the SPECT data.

DR. CALIFF: Excuse me, but less than, around 100 in each group, is the incident of P value really mean comparability or does it mean absence of evidence of difference?

DR. LAVIN: Well, just look systematically down each of the percentage attributes on page 95 and I think you will grant me parity. Looking at the key measures, CAVG 89 percent in the SPECT group versus 93 percent in the group

that did not have SPECT; AMI is 76 versus 82. Pretty consistently, pretty reliably consistent across the board between the two groups.

We also looked at outcome measures in terms of the angina outcomes and to that, we can just give our attention to the last FDA speaker who presented the data for the paired SPECT data with the angina outcomes and there you can see just by looking back about 75 percent of the patients there in that analysis also had angina relief consistent with the data that are presented here for the much larger patient population. So from my perspective, I feel very comfortable that the population is comparable in terms of baseline attributes and in terms of the outcome attributes. There is no systematic bias that I could uncover looking quite closely at the data for the SPECT users versus the patients that did not have SPECT.

DR. CALIFF: So I am going to ask Dr. Wittes for a comment but are you saying that you would recommend that as a good methodology for clinical trials that we miss half of the primary endpoint data and then try to reconstruct, that there is no difference and ascertainment is a reasonable way

to be confident that the results represent the population.

DR. LAVIN: I am speaking to the specific situation here at hand where we can look systematically at those who had SPECT evaluations versus those who did not, and I do not see any bias in terms of patient characteristics or in terms of outcomes. I would ideally like to see all of the patients have SPECT but this is a real world situation for the reasons that Dr. Lefebvre indicated, it is not always possible to have complete data for all patients at all visits.

DR. WITTES: Actually, I read this data a little differently, and I, if you look at the medical history portion, what you see is in fact each, if you slice the way you have, each piece is non-significant but if you look at the data in aggregate and say does it look as if, and I am not doing any statistical tests because I don't know which patients had more than one but if you look in aggregate and say which column looks sicker, then it seems to me those without SPECT, they have higher CABG rate, higher PTC rate, higher in AMI rate, lower CHF, higher VA, higher cardiac arrest, higher COPD and higher renal disease. So that it

seems to me on the face of it while the individual lines are not significant, it doesn't convince me that the aggregate is not.

Furthermore, I couldn't find, and I looked and couldn't find this table split by training and control group because one of the issues that one wants to know is the selection to the primary endpoint, the SPECT data, is there differential selection in the two groups and I couldn't see it. It must be here someplace but I didn't see it.

DR. CALIFF: Do you have that data broken down by treated and control group because in an unblinded study, I agree it is not just a matter of is there a bias in general but is there a bias with regard to which patients in each group came back.

DR. LAVIN: No, we do not have that.

DR. CALIFF: I mean, there is a lot of very nice work. I am sure, as you know, showing that when you have small numbers, insignificant imbalance is occurring in multiple baseline characteristics can add up to a huge difference in expected outcome of the two populations so that is a point of concern. I would also like to ask Dr.

Wittes, just while we are on this issue to comment about is there any way to deal with so much missing data other than what has been done here, particularly it is bothersome to not count the deaths in some way in an analysis of an endpoint which is short of death.

I mean, the absurd example would be if you have 95 percent of the patient dead in the treated group and the five percent who were alive were all doing great. By this method of analysis you would conclude that the treatment was phenomenal.

DR. WITTES: I would agree with you. In these kinds of data, I would have liked to have seen some analysis that incorporated the tests. But also, it seems to me, you need to do some sort, I would have liked to have seen some sort of sensitivity now on what would have happened modelling what you see within the data to impue what might have happened to those who didn't have observation so I think there is plenty more that one can do. You can't know what happened to those people.

DR. LAVIN: We did an analysis where we counted the deaths as failures. Terri, could you put that up? It

is the angina series.

DR. CALIFF: Do you have a page number?

DR. LEFEBVRE: It is the additional equations, page 3 of the angina section.

DR. LAVIN: In this analysis that Terri is finding for us, we did count all of the deaths as failures and I believe, I think we handled the deaths as failures and that gives us overall response rates in terms of the proportion with two or more improvement for the, it was 60 percent for three months, a 58 percent with a two unit or more improvement in six months and for the control group it was seven percent both at three and at six months.

DR. CALIFF: One thing we have done in other studies would be to just count all the patients lost to follow-up as having the worst outcome in the experimental arm and the best outcome in the control arm. If you did that, would the results still be statistically significant?

DR. LAVIN: Yes, they would. You would have the 60 percent would probably come down to around 50 percent with the loss of 10 percent of the patients, counting them as failures. That would be around in the low 50s and the

seven percent would come up to around 13 percent so you would have the 13 percent against like a 52 percent and I think you would grant me with the sample size of 100 per group that would be significant at less than a .01 level.

DR. CALIFF: Just as a place saver, I think that would, to me that would be more helpful to see the actual numbers there than actually anything else that you could do. In other words, if you give yourself the worst case scenario for missing data, if it is still that way and I grant you, on the face of it, it sounds that way but it might be good post-hoc to look at that more formally.

DR. SWAIN: I think he answered your question as to what to do about the deaths but you are talking about every missing data point so if you actually added every missing data point of the 66 percent that didn't have imaging, would those numbers be significant?

DR. LAVIN: Well, the numbers that would be significant would be counting the 11 and the 8 patients who did not have the angina evaluations at three months. If one counted those in, those are the calculations that would give rise to the 53 percent and 12 or 13 percent for the control

group and the other group, the TMR group, so there would be a significant difference if you counted the losses as failures as he was suggesting.

DR. CALIFF: Let me move onto another. There are the numbers there.

DR. LEFEBVRE: Actually, that is the slide when the additional procedures were counted as failures. There is another slide for death and there is another slide where additional interventions were counted as failures.

DR. SWAIN: Do you have a similar one for this fact?

DR. LEFEBVRE: No, don't.

DR. CALIFF: On the statistical issues, your significance value for all the comparisons is .05. Is that true for all comparisons that you did and what would be the rationale for that if you have multiple comparisons being done?

DR. LAVIN: Well, when you have, it depends on how it is framed. It depends on where you come from in terms of studies with multiple endpoints. It is my position and the one that was taken on the protocol when it was originally

prepared that a significance level of .05 was being used, even for assessment of multiple endpoints. We did specifically control the evaluation of the same endpoint at multiple times by using a proc-mixed model approach that allows us to obtain one P value in comparing the data across all of the different time points.

So, for example, in looking at the reversible defects, there we did one simple test of significance and compared the two treatment groups in the phase three study. For the angina data, we also addressed that problem by looking at an outcome or the last evaluation so that each patient would only then count once so in both situations we addressed the situation of multiple testing by the strategies of the last observation and also from a longitudinal data analysis approach.

DR. CALIFF: And that would hold for all the endpoints you looked at. Is that 10 or 20 or 30 different endpoints? You would still accept .05 for each one?

DR. LAVIN: Well, we looked at the two primary and we also looked at the other endpoints, the quality of life measures in that same manner.

DR. CALIFF: The blotting and interview technique. We all know that it is very difficult to blind a surgical study obviously but one thing that can be done is to blind the interviewer to the treatment. What measures did you use to train the assessors of the, I think in the protocol it is actually a secondary endpoint of angina.

DR. SWAIN: Anybody take a stab at that one?

DR. LEFEBVRE: We, the only blinding that took place during the study was with respect to the SPECT study. The readers were blinded as of the treatment group. They did not know that the patient was a controlled patient, a crossover patient.

DR. CALIFF: That is well delineated but the angina assessment I think is really critical here.

DR. LEFEBVRE: I think someone else can talk to you better as to how the assays for angina.

DR. SWAIN: I think it was answered that there was no blinding?

DR. LEFEBVRE: There was no blinding.

DR. CALIFF: But it is not just blinding. There are also multiple studies that have been done with trained

interviewers who are careful not to bias the patient's response.

DR. LINHARES: Could we ask Dr. Lansing maybe to address how we analyzed the patients?

DR. LANSING: Dr. Lansing from Louisville. At our center, and I can't speak for all of them, the patient himself fills out these questionnaires with no help or guidance. Only the family member sits with him. The clinical coordinator presents the papers to them, leaves, comes back and picks them up afterwards so yes, they know where they were treated or not. It is up to them to decide the answers to all the questions.

DR. CALIFF: But Canadian class would be very heard for the patient to fill out.

DR. LANSING: He usually does, as a matter of fact, and if he has questions about this, then the clinical coordinator will help him to decide whether he is class two, three or one, whatever he is but basically we let him decide whether he is stable or unstable and it is listed there what is involved in zero, one, two, three and four on the evaluation sheet and the patient and his family fill that

out.

DR. LEFEBVRE: Maybe we can have a few other investigators tell you how they assessed angina.

DR. CALIFF: If I can hear a couple of statements about this.

DR. COHN: I am Lawrence Cohn, Boston. That was pretty much the way we did it. Obviously the clinical nurse-coordinator is employed by our division so from that standpoint it can't be blinded but she would hand the forms to them and I would not be involved in any way whatsoever in filling out, talking to the patient about this until they sat by themselves and the nurse coordinator coordinated the forms and then I saw the patient. It was all done before I saw the patient.

DR. CALIFF: So there wasn't a systematic study-wide approach to interview technique for assessing angina but obviously it sounds like the investigators each had their own way of dealing with it.

The last area, just to touch on and we can move on to other questioners is the area of morbidity. The data

obviously shows among the patients in whom it was assessed that angina was less common in unstable angina. It was less common but at least as I looked at the adverse events, it looked like there was about a threefold increase in serious ventricular arrhythmias and at least a doubling in heart failure in the patients randomized to the device and it is hard for me to focus on one area of morbidity and not pay attention to the others.

I wanted to get the point of view on whether statistics were done on those important areas, how you viewed it and also how those outcomes were assessed. I have been trying to look through the case report form quickly. Was it a check box where each patient had those endpoints assessed or was it a free form, fill in the blank kind of adverse events form?

DR. LEFEBVRE: In phase three there was a specific adverse event form which listed all of the expected adverse events observed, thought to be seen in the study. Those were check boxes and beyond that there were some comment areas that had to be listed as to what was the severity of the adverse event, was it life threatening or not, what was

the reservation of the event and so on and so forth. There was one adverse event used for each adverse event.

DR. CALIFF: Did I get the data right about the ventricular arrhythmias and the heart failure?

DR. SWAIN: On page 15? I am sorry, that is phase one. Where is the phase three morbidity?

DR. LEFEBVRE: Phase three is page 117.

DR. CALIFF: There is actually a very succinct table in the FDA part that, well, anyway, even if we go to page 117.

DR. LEFEBVRE: It should be 117 is the incident of the time. The actual numbers are listed on page 111.

DR. CALIFF: It is a life threatening arrythmia looks like about 18 percent over six months and heart failure about 18 percent. And the intent to treat group I guess laid out there some life-threatening arrythmia and heart failure laid out. So there was a check box in phase three. IN other words, each patient was specifically, for each patient the coordinator was specifically asked, it wasn't a generic sort of fill in the blank from what you thought the patient had.

DR. LEFEBVRE: Yes, the coordinator had to indicate if there was an adverse event and if there was an adverse event, then the study coordinator filled out the adverse event form which went into detail about what type of event it was.

DR. CALIFF: I have two more questions related to morbidity. The first one relates to slide number 28 on your presentation, the mortality curves. It might be worthwhile to put that slide up if we can do it quickly.

I have a concern here related to characterizing what the trade-off is between the potential for better angina status and mortality and as I understand it, the blue curve there is the group randomized to TMR or the yellow curve I guess would be the phase three. The red is a control. There is a pay value of 0.16 for phase three TMR versus control. Which group does that P value favor? It is a trend.

DR. LAVIN: It is a global test of differences between the shape of the two survival curves. It doesn't necessarily favor directionality one or the other.

DR. CALIFF: Okay. I guess the difference between

phase two and phase three is fairly substantial in terms of characterizing the early risk and I know we will get into a more broad discussion of that but I just wanted to make sure that that was viewed. If we only had the phase two results, it would be hard to characterize that as no risk with the phase three results, I don't know whether I don't exactly have to look at that.

The final question is related to this question of myocardial infarction. Obviously it is hard to characterize the very procedural myocardial necrosis but you seem to be making a claim that there is a reduction in non-fatal infarction and follow-up but for me it is hard to put that into perspective when there is a perioperative mortality and there are things happening related to loss of myocardium at the time of the surgical procedure.

I guess there are two questions. One is did you measure enzymes or anything else to tell you about the amount of myocardial necrosis at the time of the procedure and secondly did you make any measurements of resting left ventricular function in the two groups?

DR. LINHARES: Dr. March, would you like to talk

about that?

DR. SWAIN: Bob, why don't you use the podium.

DR. MARCH: Robert March. The question was did we ever measure any injury related with enzyme evaluation and early in the phase two study, we did measure serial or cardiac enzymes around the time of operation and they never became significantly elevated to suggest actual injury as far as CB can rise.

DR. CALIFF: What is your definition of significantly elevated?

DR. MARCH: Depends which index you are using. But what would be considered significant in the lab, our hospital uses CPT NB index and anything over seven is considered injury and we do not have a consistent pattern of injury if you will. We had CPK NB rise because there was a thoracotomy but the NB index never was significant in the phase two patients that we had performed the study on.

In regards to baseline left ventricular function, we used transesophageal echo routinely throughout the procedures and if here is any adverse event throughout the post-operative period, we will reinsert the probe to see

what might be happening and we have not seen any deterioration, at least not transesophageal in regards to function. As a matter of fact, if it is not in the panel packets, I don't know if I could speak of it but abstract submissions from our hospital as well as others have not shown a deterioration in ventricular function from laser heart surgery, baseline compared to three, six and in our series 12 months follow-up. We have looked at modus scans in 17 patients that are one year out and there is no difference in injection fraction, no improvement and no diminishment in function.

DR. SWAIN: Dr. Califf will have, I am sure, a lot more questions for the next round. We appreciate the careful analysis. Dr. Edmunds.

DR. EDMUNDS: I recognize that you have got a difficult burden here in terms of dealing with angina which is a subjective symptom and thallium perfusion scans which are a little bit more objective in some ways but on the other hand, you have to get down to looking at segments on very, very small drawings and then the third is that your quality of life assessment which is clearly subjective so

that you don't have any clearly objective numerical kind of endpoints in this study.

Now, as a point of clarification, do you have the operative mortality on those Kaplan Meyer mortality curves? Is that included on there?

DR. LEFEBVRE: All mortality included. The operative mortalities are included in the curve you have seen on the screen. In the panel package there is another curve that at least the follow-up mortality when you exclude the death that occurred within the first months after surgery but that, the curve that you have seen included all that.

DR. EDMUNDS: Okay, thank you. Do you have any idea as to why the arrhythmias are a little bit more serious than the treated group as the untreated group? Do you have any idea about mechanisms or any additional information?

DR. LINHARES: We would like to have Dr. Horvath answer that.

DR. HORVATH: I think the incidence of arrhythmias that you see is somewhat part of other complications. For instance, if the patient did have an acute MI, they might

also have an arrythmia at the same time. Those were both listed as adverse events for that patient. We did not, aside from those combinations, did not see, at least in the patients that I treated, see an increase in life threatening arrhythmias.

DR. EDMUNDS: But the data show that there is an increase in the treated group.

DR. HORVATH: The data shows that and I, the data shows it I think in regards to combinations of numbers of complications. As sole complications, we did not see that as an isolated adverse event.

DR. EDMUNDS: I don't quite know what you mean by that but I will --

DR. HORVATH: I think what I am saying is that patients can obviously suffer more than one complication after the procedure. And we saw life threatening arrhythmias as part of a complex, acute myocardial infarctions, et cetera, did not see life threatening arrhythmias as an isolated event related to the procedure.

DR. EDMUNDS: I see. Well, I share a lot of the concerns about the methodology and the diffuseness of

endpoints and actually the objectivity of evaluating the endpoints but I would like to talk a little bit about mechanisms or at least inquire of the mechanisms. Do you have any evidence that you actually are treating hibernating myocardium rather than non-hibernating myocardium?

DR. LINHARES: We would like Dr. Frazier to address that.

DR. FRAZIER: Bob Frazier from the Technical Institute. This group came to us in the early 1990s with this proposal. I actually knew none of the participants. Our chief, Dr. Cooley, knew them but I did not know any of the participants and one of the things I insisted on, being well familiar with the history of this extra-anatomic blood flow to the myocardium was that the company pay for carefully documented PET scans to address just the issue raised, to do sa accurately as possible a study to reflect improved perfusion in this patient group and they agreed to do that.

For whatever reasons, PET scans, I am sure panel members are familiar, are not readily available because of mechanically they are not available in most places,

logistically rather, and we have the good fortune in our medical center to have one of the primary investigators in this field as well as a cyclotron and the ability to do these studies and I think that it is clearly the best way we have of non-invasively assessing perfusion or the best way we have of assessing perfusion.

So they agreed to do that and we studied 12 patients. Let me have the first slide there. This is an example of one of the patients. Obviously the first thing we had to do was demonstrate that there was, as alluded to by ability of the myocardium. This was done with the glucose isotope and --

DR. SWAIN: Excuse me a second. One, we can't see it, we need the lights down. Two, Bud, is this in the packet?

DR. FRAZIER: Yes, the paper is in the packet. And I think this is a good reflection of one of those patients and you see on the top the perfusion deficit, particularly in the third view, in the anterior lateral view as a significant deficit and in the lower view you see the glucose which demonstrates that this was, in fact, viable

myocardium. Do you have any questions about that?

DR. EDMUNDS: Yes, do you want to show me the other 11 patients?

DR. FRAZIER: I can show you the results of the other 11. This is obviously the one that it is very clear on. We just did the myocardial follow-up. This is another patient that shows again the deficit at the top with the perfusion deficit. Twelve months later, you see the improvement in the perfusion demonstrated no the PET scan. This is only the ammonia isotope.

Another similar 12 month study that demonstrates the improvement, this is 12 months after treatment with nothing but the laser, an improvement in the perfusion status on the PET scan compared to the view on top.

We didn't specifically study viability but this is, and I don't think we have the claims to support viability at all right now but I think this does demonstrate one of the patients that we followed viability at 12 months and there was some improvement in the myocardial viability from the top to the bottom.

Now, to study this we specifically tried to look

at the ratios. Obviously you are not going to improve the flow to the epicardium since the epicardium chamber blocks off in the operation, in the bleeding stop so we had to assess the endocardial perfusion with the PET scan which is possible to do with this technology.

I think this is one of the studies that demonstrated comparing again these were their own controls, pre-operatively on the left and post-operatively on the right, a general improvement in perfusion in the endocardial sub-regional of the myocardium.

Angina class I think which wasn't a part of the study, I am sorry, the angina class was part of the study and we had the same reflection in this group of patients as an improvement in angina class but we also saw a definite improvement in time on the treadmill as you can see from baseline 12 months which is something that is not subjective to patient interpretation.

I think I don't want to go through, this, I think, is an attempt to address some of these with the patient. I think you are going to find the slot of a summary of the sub-endocardial perfusion studies to address Dr. Edmunds's

question.

We found in 11 of the 12 studies we followed there was demonstration of improvement on the PET scan of a sub-endocardial perfusion.

DR. EDMUNDS: Was there a demonstration of a hibernating on myocardium preoperatively on all of them?

DR. FRAZIER: On all of them. They had to have viable myocardium on the glucose prior to that.

DR. EDMUNDS: You are the only one to have published an autopsy of a patient who is treated at three months and in that you found that the laser channels were open but they were one-tenth the size they were when they were made. In other words, they were down less than 100 microns and they were 1,000 microns when made.

DR. FRAZIER: I think that data, and I really do take issue with the statement made by the FDA presenter that there is definite, proven evidence that they are not open at one month. That actually there is not proven evidence to that effect. I will take issue to all the papers that are presented in that, not that there is or there is not, I think it is still out. The things that we do show which are

important to me clinically are an improvement in sub-endocardial perfusion. And the, if you look at these holes, I don't know, you can take the same pathologist and look at the same slide and one of them will say it is occluded and the other will say it is open so I don't have much credence in that.

I think clearly there is some improvement in the profusion in the selective group of patients, that is, patients with chronic coronary artery disease and preserved ventricular function.

DR. EDMUNDS: Bud, you are basing that on your PET scan studies and on the thallium perfusion scan studies that the sponsor has presented to the panel.

DR. FRAZIER: My feeling mainly on the PET scan, thallium is a --

DR. EDMUNDS: And you have presented that to us but now I want to go into the, there are only two autopsies that I could find in the case reports of patients who had been treated, one at two months and your patient at three months and in both of those it showed scarring along the channels and it showed an inflammatory reaction that was two

or three months old. Do you disagree with that?

DR. FRAZIER: No, I think that is what it does show.

DR. EDMUNDS: Does anyone from the sponsor have any evidence to show that angiogenesis is occurring after this treatment?

DR. LEFEBVRE: Actually, what we have is we have some --

DR. LINHARES: Dr. Crew has done some interesting experiments and we would like him to get up and present.

DR. LEFEBVRE: And this data is not in the package but it was in the PMA submission.

DR. CREW: John Crew from San Francisco. We share the same concerns as to the validity of the holes that have stayed open or whether they didn't stay open. We initially did a study in rabbits where we used the Mercox infusion into the ventricular chamber to force that out the holes and to look at that as a value. These were non-ischemic hearts and it was a difficult one to complete. But I have had the privilege now of using this same type of testing on two patients, one which I will show here and that is that the

patient had a very successful TMR as measured by his status questionnaire, his lack of angina, his drop of medication and his thallium studies which have returned to normal.

We then took this patient who was six months post-TMR, died of a brain stem stroke up in Yakima and had his heart sent back to Dr. Knight at the University of Minnesota and he infused this heart with Mercox and you can see the infusion. Unfortunately we took formalin, we formalized the heart because we were afraid the holes would stay open, wouldn't stay open or for some reason or other, and this made it very difficult. IT took six weeks to ingest the heart away and what you see here is the right part which is blue is the Mercox infusion and you can see vein channels on the left side, next to --

DR. EDMUNDS: Point those out. What is Mercox?

DR. CREW: Mercox is a substance that is very fluid, just like blood and when it is activated as a polymer it forms a rubbery substance that is not, that is immune essentially to any type of digestion or things that would do that and so you can force it where all the blood went and let it sit and that hardens and you digest the heart away

with decimen hydroxide or sodium dihydroxide or some lye digestant that will take it away. Unfortunately, when you formalize it, it cross-links the collagen enough so that it is very difficult. This took six weeks. This particular one took six weeks.

And so what we did then is we took his heart and we force Mercox into the ventricular chamber only where the competent mitral valve and an aortic valve are secluded. And here you can see --

DR. EDMUNDS: What was your pressure?

DR. CREW: That pressure was probably about 200 millimeters of mercury and we forced it and let it sit for awhile and then let it harden and then spent six weeks digesting away, and this is partially digestive heart that you can see down in the corner. This is complete digestion and this is what you see then. This is the Mercox that shows the negative outline of the inside of the endocardial surface and you can see a small amount of what you are going to see in the last slide.

This is essentially a picture of six months and these are the sinusoidal, the holes are multiple holes in

this nest along in here that are supplying the sinusoidal area in that area and then it gets together and forms a venus outflow structure that goes away and the bigger one is a vein where the drainage away.

We wanted to see if the holes were significant and stayed open. I think this fairly well shows that it did. I did it on another patient the same way and we got essentially the same results.

DR. EDMUNDS: Do you have any controls?

DR. CREW: No, I don't have any controls.

DR. EDMUNDS: I think that you probably pretty much need then, don't you?

DR. CREW: I think controls in this situation would be very difficult to obtain.

DR. EDMUNDS: I think that pretty slender proof of angiogenesis, don't you? I mean, this is, we are really talking about, I have always been taught, at least the experience that the heart is mostly a lake of blood in which a few myocytes are embedded and you are showing me that it is a lake of blood.

DR. CREW: But I am showing you that what we felt

were the holes that were connecting from this lake and putting into the lake of blood but this doesn't address angiogenesis. There are other ways to address that and we are trying to look at that, addressing angiogenesis in hearts like this.

DR. EDMUNDS: But this is your data so far.

DR. CREW: Yes, sir.

DR. EDMUNDS: Thank you.

DR. LEFEBVRE: We wold like to have Dr. Cohn make some additional comments.

DR. LINHARES: By the way, that is outlined in the panel package on page 194.

DR. COHN: Lawrence Cohn, Boston. To answer your question about the channels is the one that has bothered everybody for a long time and I don't think there is a definitive answer. I do think there are two pieces of evidence that support one, hibernating myocardium and two, some experimental work which is not included in your package that was presented at the surgical forum last year and will be presented again this year in which we at our laboratory, our fellows, created a model of chronic myocardial ischemia,

a porcine model, and with controls, laser anomalies are show a marked increase in sub-endocardial profusion by an angiogenetic response like markedly red blindly.

It may be that they are like any one of these devices that have ever been measured in the history of the world, there may be species different. In other words, in the porcine model, the channels were not there, angiogenesis was extremely profound. It may be in the human responses that we don't know and that obviously an important area.

The other area, the hibernating myocardium in clinical studies I think is in the package. It was presented by a member of Dr. Califf's department, Carolyn Donavan using a stress echo with the butamen. It did show improvements in the wall motion and areas that were laser were previously, they had not been. So those were the only two pieces of evidence I wanted to bring to your attention.

DR. EDMUNDS: But it showed improvement in wall motion, Larry.

DR. COHN: In wall motion, right.

DR. EDMUNDS: Just segment by segment. I didn't see that in there but maybe others did.

DR. COHN: That was a stress echo.

DR. EDMUNDS: My question is, why isn't this just a non-specific inflammation that is created by this high energy beam? Do you have any evidence that this isn't just a non-specific, are you just inducing some scarring where the holes go?

DR. LEFEBVRE: I think we would like Dr. Horvath to comment with respect to some studies that he had conducted and others have conducted.

DR. HORVATH: To go back to your previous question about autopsy studies, there is published work from Germany on specifically your question. Various autopsies add a few days to several after having the laser procedure. In those studies they did document angiogenesis. It was interesting that patients who did not have a clinical success, did not have a tremendous improvement clinically also did not show a tremendous amount of angiogenesis or tremendous evidence of channel patency.

DR. EDMUNDS: Keith, I don't think it is in here.

Dr. HORVATH: It is not in there. But you were asking as far as autopsy studies, if there is anything

available.

Likewise, there has been echocardiography performed on patients at our institution and at others that demonstrate flow through the channels by doppler signal. These have been done interoperatively and as well at an average of 280 days. Again, I apologize. These date are not included in the package.

DR. LEFEBVRE: Actually, that data is the data from Germany. We are getting the reviewers and he is included in the PMA.

DR. HORVATH: And in those studies in patients that were treated with the laser, there is evidence of systolic and diastolic flow for that matter through the channels early and late.

DR. EDMUNDS: Do you want to tell me what hertz those echocardiograms were taken in order to demonstrate one micron channels?

DR. HORVATH: Three and a half to seven megahertz.

DR. EDMUNDS: I don't think you could see them. Are you sure?

DR. HORVATH: The Accuscience at Sequoia 512

system has that kind of resolution. With contrast and without contrast.

DR. EDMUNDS: But on the data here that we have, and I don't know that you want to answer this, on page 431, we have the six month comparison of the angina and the perfusion scan. Dr. Califf has gone into his concerns about the fallout of the data, the lack of complete data, both angina as well the thallium but I see here at six months which is the most data you have, correlating the angina with perfusion and basically you have 16 who are better and 12 who are worse and to me that is a push.

Now, can you enlighten me? In other words, I don't see where you have demonstrated efficacy on this diagram, the lower one, the six months data when you compare symptoms in thallium perfusion scans. They don't correlate. Am I not interpreting this correctly?

DR. LAVIN: Philip Lavin. I think what you want to look at there depends which way you are looking at that table. What I look at there is the change in the angina score and I am seeing at least 70-75 percent that have improved by at least two units and you want to look across

the rows to see that.

DR. EDMUNDS: Well, Dr. Lavin, I am looking at the blocks, one on the right and one on the left, all below the no-change line, and there are 12 on the right and 16 on the left.

DR. SWAIN: The panel, this is in section four, page 31, kind of at the beginning of the packet.

DR. EDMUNDS: I think using, with the caveat of the methodologic concerns about the objectivity of analysis of the angina, having surgeons get data from their patients and presumably cardiologists get data from the control patients and so on, I am just looking at this data here --

DR. LINHARES: I think we need to explain the table.

DR. EDMUNDS: Maybe you do, yes.

DR. LEFEBVRE: The data, as was explained by Dr. Chandeysson, exploded on the bottom axis. You have the changes in number of ischemia defect and on the vertical axis you have the change in angina classes and what the correlation that was shown, the concordance that was shown looks at for those patients who experienced a clinically

significant improvement in angina, was there a change in perfusion and therefore that box is not exactly the box shown here. Okay? It is not the box at the bottom of --

DR. EDMUNDS: It is not exactly the box shown there because the right lower one is the ones where they have improved their angina but the perfusion is not as broken.

DR. LEFEBVRE: No, no, that is the other way. We are looking at it the other way. A decrease in perfusion defect, minus one, minus two, minus three indicates that there was a reduction in ischemia so that is good.

DR. EDMUNDS: Yes, that is on the left hand side. On the right hand side, they are plus one, plus two, plus three, and that means that the perfusion is worse.

DR. LEFEBVRE: That is correct.

DR. EDMUNDS: Uh-huh, and 12 patients had worse perfusion but better relief of angina and 16 had better perfusion and relief of angina.

DR. LEFEBVRE: But what you have to look at is what was considered to be clinically significant from an angina standpoint and that was the reduction of two angina

classes.

DR. EDMUNDS: I am having difficulty then, assuming angina to decide whether the PET scan or the thallium scan is better or not. In other words, what I am seeing is there is very little correlation that I can see on this diagram between the perfusion input and the relief of angina. The angina was relieved in half of the patients without an improvement in the perfusion.

DR. LEFEBVRE: If you look at what was considered to be clinically significant, that correlation changed, there was a 60 in phase three at 300, there was a 68 percent correlation so yes, there were on the other end 32 percent of the patients for whom the angina success did not correlate with perfusion.

DR. EDMUNDS: I will reset my case there I guess.

DR. SWAIN: We will just go for a while longer until we all get hungry. Head around the panel. Dr. Casscells.

DR. CASSCELLS: This is a difficult procedure to analyze but clearly one that is relevant and driven by the best motives. There are people who do have refractory

angina and there are trials being started now to use angiogenic growth factors for these patients despite the improvements in angioplasty there. There are some lesions that can't be dilated and so forth.

There are a number of issues that I have. I will try to be brief. On the one hand, it is possible that you have understated the data because the crossovers to therapy, depending on whether you analyzed by intention to treat or not may indicate the benefits are even greater than you have gotten but we have got to deal with this lost data and some of the subjectivity issues.

I threw in a concern at the percent of patients lost to follow-up and the percent of patients in particular who didn't get imaged. I am concerned as well that there was no independent data safety and monitoring committee. As an editor on numerous journals, we would find it difficult to publish follow-up studies that did not have 90 percent follow-up and where the endpoints were not predetermined. It is very important to predetermine the endpoints and to have these be registered with the data safety and monitoring committee who are completely independent of the company.

Then you can get back to me about that.

It is very important that the endpoints be predetermined and that other endpoints, if they are collected along the way, be reported. For example, Dr. Frazier showed very nice data on the treadmill timed duration and that is an important data point. It would be nice if all the centers could show what happened with their treadmill duration and with their ejection fractions, either rest or ideally rest and exercise ejection fractions.

Posses an important data point. It saves you from this kind of perspective analysis which was not in the package in your PMA application. It saves you from the criticism that you may have been looking at numerous endpoints and ended up showing us the endpoints that looked good, the angina and the thallium data.

I share Dr. Califf's concern about the bonferoni(?) problem when you are looking at multiple endpoints. You really ought to take that P of .05 and divide it by the number of endpoints you are looking at. On page 422, you state or the FDA states, rather, that about half the time the angina status was determined by the

nuclear medicine physician who half the time was determined by the surgeon. It does not suggest that the patient's self-scoring questionnaire was ever passed through directly. I think you need to look at the number of times that the patient classified himself as done in Kentucky and give us that data. That is very solid data, certainly less susceptible to subjective influences. Patients want to please the doctor, as you know. We have to guard against that.

You describe in your presentation that there were more myocardial infarctions in the control patients. This is one of your data endpoints, and yet in your perfusion, you show no thallium perfusion defects in the control patients or no increase in defects. If the patient is with, if the control patients were experiencing myocardial infarctions, this should have shown up as a defect, a fixed defect on perfusion scanning.

You have about 17 percent of patients who have no baseline ischemia and 12 percent of patients deteriorated and underwent bypass or angioplasty. Since the admission criteria required inoperable vessels or other regions for

inoperability, it seems that some patients got in who were not that sick. They may have had angina class three but if there was no ischemia on the percent in thallium, and they were subsequently operable, I think you should re-analyze the data of removing those patients. That amount of 29 percent of the patients.

I think the results would still be similar but it makes your analysis more robust if you could do these kinds of alternative analysis, sensitivity analysis.

You described that the patients became virtually free of angina. Most of them end up class one after TMR. But it would be good to see the raw data on the scans. You show data compared to baseline, looking at 12 segments, you show on average one or two segment improvement in reversible defects. My question to you is did patients still have reversible thallium imaging defects? Have you created a group of patients who have silent ischemia, in other words.

I am interested in the pathology. The pathology there looked to me like Venus lights with besium veins. I share Dr. Edmunds's point that number one a perfusion pressure of 200 is rather high for a postmortem study like

that and number two, it is relatively easy to get non-lased hearts to see if you can see pictures like that.

The perfusion data from the PET scans is impressive. The main architect of that work, Dr. Gould, is not an author and it would be good to know why that is.

There are some remaining engineering issues that are listed earlier and I think you probably resolved them by now.

I think the most important issue, though, perhaps, is what other therapies might these patients have gotten? If indeed after TMR, the patients are going off their drugs and yet doing awfully well, this is indeed a very, very exciting therapy. On the other hand, we have to guard against the phenomenon in patients who have had surgery, changed their lifestyles in dramatic ways. Patients who have had surgery often lose weight, they tend to be entered into cardiac rehab programs. These are very effective programs. There are actually 22 randomized studies of cardiac rehab and the net improvement and mortality is about 25 percent so cardiac rehab saves lives.

Patients who have had surgery typically stop

cigarette smoking. It would be important to know what has happened to your patients in that regard.

Compliance is often better after surgery. It would be very important to know how many of your patients are taking cholesterol lowering medications, how many of them are taking their beta blockers, how many of them are taking their nitrates, their aspirin and so forth. A few or your patients may have had an AICD implanted. A few may have had pacemakers implanted. These are adjunct therapies which were not randomized. This is, now if this were the case, that is a worst case scenario. It is not an argument against your device per se because the strategy of putting in such a device may lead to these ancillary benefits when it ought, we ought to be clear what is a benefit of the device per se and what is a benefit of surgery and the intense medical follow-up, the trips back to the doctors, the rehab, the patient education and so forth.

And very importantly, there is a psychological benefit finally and when patients have gotten through surgery, there is typically a period of relief and euphoria and you showed in your data in the presentation, a dramatic

increase in satisfaction. Satisfaction with therapy. And this very often goes on to indicate a real, to confer a real mortality benefit. I think we must recognize now that there are over a dozen studies showing very clearly that optimistic attitude improves survival and depression infers now we think now when we think a four to five-fold risk factor for death.

So if in the process of operating on the patient and surrounding that patient with research nurses and doctors and doctor visits and a lot of enthusiastic media reports and so forth, we have to recognize that part of the benefit I think is strongly subjective though real. It is caused by this tremendous boost to the patient's confidence and so forth.

So these are a lot of questions and I will repeat them in order if you like. I would like to get answers on all these.

DR. SWAIN: Why don't we, why don't you just rank them and ask one question and we will get one answer and we will keep going.

DR. CASSCELLS: Would you first address the issue

of the myocardial infarctions? You state that there are more myocardial infarctions in the control patients. It is part of your combined endpoint and yet there are no proof, there is no increase in fixed perfusion defects in those patients that I could see.

DR. LEFEBVRE: As a result of the high attrition rate that we have already talked about a lot, we actually looked at those patients who had an AMI and tried to see if there was a change in fixed defect for the SPECT studies. I believe there were three patients with SPECT data available in phase three. That is all we had so that such small numbers is not, does not permit to draw any sort of correlation between and the incidence of an AMI or an increase or change in SPECT defects.

DR. CASSCELLS: You don't need to have enough statistics to prove it but I think if you define an MI as something that doesn't show up on a thallium scan, you ought to be very clear about that. If a person has a component T of 0.1 or a CPK of 200 or something like that with three percent MD, then that could be called an MI and yet your standards that one of your staff, your investigators

mentioned for calling an MI a procedure was a seven percent MD, for example. Maybe a two or there fold increase above baseline.

So it is very important to have a fixed definition of myocardial infarction at the beginning of the study to apply that definition to the procedure and to the outcome events so please look back and let us know if the patients you say had a myocardial infarction had a thallium defect.

What about your other endpoints? What is your aggregate data on left ventricular ejection fraction and your aggregate data on treadmill time performance or ST segment slope on the treadmill?

DR. LEFEBVRE: Exercise was not a study endpoint. The study endpoints stated in the protocol were decreasing ischemia as measured by SPECT studies and angina relief. Additionally, the study endpoint stated in the protocol were quality of life so we did not look, some of the individual centers looked at treadmill times but that was not a study endpoint.

DR. CASSCELLS: What did they find?

DR. LEFEBVRE: I think Dr. Kadipasaoglu or Dr.

Frazier can comment on that.

DR. CASSCELLS: We have seen Dr. Frazier's data. That was most impressive, as I mentioned. What do the other centers find in treadmill time?

DR. LEFEBVRE: Dr. March, do you, Dr. Lansing would like to comment.

DR. LANSING: Thank you. I would have to say that our patients could not do a treadmill exercise test to begin with. They were all class four, at least 40 percent of our patients were unstable or actually pre-infarction. That is, they were on IV, heparin, and nitroglycerin for a week or more. These patients cannot do a treadmill exercise test so, and to do one later would not be of any help. So unfortunately we were unable to do them because of the type of patients we were dealing with.

DR. CASSCELLS: Well, late treadmills, Dr. Lansing, are possible. You can compare the TMR group to the non-TMR group. That would be helpful data if you did have it.

DR. LANSING: Well, we could have prepared a year to three months as well so yes, you are quite right.

DR. CASSCELLS: It should be very easy, even today, for your statisticians to look at the actual thallium data. Your patients in whom angina pectoris was abolished, do they still have residual, reversible, do they still have reversible thallium defects? I don't think you can answer that now. That may take several hours or several weeks to add that up.

DR. LEFEBVRE: Could you please repeat the question?

DR. CASSCELLS: You had a dramatic fall in the amount of angina pectoris. What happened to the reversible thallium defects in those patients? You have only shown a decrease compared to baseline in one segment out of 12. What was the, for example, did your average TMR patient have five ischemic segments pre-op and four ischemic segments post-op? That would indicate that you have patients in whom angina was abolished but they still have lots of ischemia.

DR. LEFEBVRE: The, on page 95 of the printed package, you have the preference studies of the patients at baseline.

DR. CASSCELLS: I am sorry, page 95.

DR. LEFEBVRE: Ninety-five, yes. The average number of reversible defects at baseline ranged between 4.0 to 4.8.

DR. CASSCELLS: Okay, thank you. That is very helpful. I want to see if I can follow that along. You are looking at the bottom, phase three, and the free wall and the fixed defects, this is pre-op.

DR. LEFEBVRE: That is a baseline pre-op.

DR. CASSCELLS: I think 5.7 is baseline. It doesn't say baseline.

DR. LEFEBVRE: All right, perfusion studies at baseline, that is the title.

DR. CASSCELLS: I am sorry. So the reversible defects were 4.8 in the TMR group, 4.4 in the control group. Where is the post-

DR. LEFEBVRE: Post, you have to look at, there are approximately 30 pages of analysis because we looked at TMR versus control, we looked at TMR versus intent to treat, TMR versus control and no crossover and one of the statements that you made when you were asking the question was that there was not perfusion in the control patients.

If you look at the change in reversible defect in the left heart for the control patients, you can see that whatever group you are looking at, there is a worsening in the number, there is a worsening in perfusion and an increase in the number of reversible defects.

DR. CASSCELLS: I have trouble following you. How about after TMR? How many reversible defects did the average patient have?

DR. LAVIN: It came down by an average of about one reversible defect for both the left heart as well as the left ventricular free wall.

DR. SWAIN: You went from five to one? No, you went from five to four. So a 20 percent change or less.

DR. CASSCELLS: So angina comes down by about 560 or 70 percent but the improvement in thallium defect size is about a 20 percent improvement.

DR. LEFEBVRE: That is correct.

DR. CASSCELLS: This may lead, when Dr. Howe made his presentation at the American College of Cardiology a few months ago, it was summarized in this week's issue of Circulation. Dr. Howe said that the imaging improvement was

not significant. You got a lot of numbers here. You analyzed them at different time points. Looks to me like the three month data was not significant and more recently it may be significant. At least using a single .05. Is that why you say this is significant and Dr. Howe said it was not significant? He was reporting on 161 patients or something, according to this week's Circulation.

DR. LEFEBVRE: We are not familiar with the study you are quoting.

DR. CASSCELLS: This was Dr. Howe's presentation on behalf of your group at the American College of Cardiology, at least it was on behalf of about 161 randomized patients and angina was relieved but there was no significant improvement in perfusion. Is that data not part of the package?

DR. LEFEBVRE: Excuse me, Dr. Lowe?

DR. CASSCELLS: Lowe, I am sorry, not Howe, Lowe. I wrote it down Howe, not Lowe. Is he part of your group?

DR. LEFEBVRE: He is an investigator at Duke. He is unfortunately one of the few investigators who is not here. That data that you presented is included in the

package.

DR. EDMUNDS: That is Dr. James Lowe, isn't it?

DR. SETHI: The person you are talking about at Duke is Jim Lowe and not Hal Lowe.

DR. SWAIN: We got that down but the question is that data is part of the packet and Dr. Casscells has a question about the findings in that data.

DR. LEFEBVRE: It is just, the analysis that we were showing at that meeting was earlier and at that point the number of scans that were used for the analysis was lower than that and as a result you are correct that there was no significant change at three months. Correct.

DR. CASSCELLS: One of the most important issues is almost a philosophical issue but it is very important clinically. What happened to these patients after TMR and what happened to them after they were, after they got a coin flip that said No TMR. What medicines did they take? How much weight did they lose? How many of them complied with their medicines? How many of them may have had a pacemaker or an AICD?

DR. LEFEBVRE: We would like Dr. Boyce to answer

your question.

DR. BOYCE: Steven Boyce, Washington, D.C. Going back to a couple of questions that were addressed before, first, the issue with the angina classification. I think that is a very pertinent issue. At our institution at least we had a what I feel to be as impartial as we can a person that is a cardiologist associated with the hospital independent of the clinical trial itself grading the angina classification.

In our own series of patients, we did not see a significant difference in the patients treated with TMR or with the controls in terms of issues with compliance, weight loss, change in cigarettes, et cetera. We must remember that at least in our experience, 90 percent of the patients we treated had already had bypass surgery and actually many of them had two previous bypass operations. So this is different than taking someone who comes in, has never had bypass surgery, any type of cardiac surgery and expecting them to seek, expecting to see the same type of modification in risk factors afterwards, once they have to deal with this acute life threatening problem.

In my experience, in dealing with these patients, and we have evaluated over 300 patients in Washington, is that most of these patients are very in tune with their health. Very few of these patient are active smokers and they are coming to Duke to see us simply because they have not been able to have any type of other remedy to their problem so for the most part, expecting them afterwards to get into cardiac rehab and have different changes such as that affect their outcome I think is --

DR. CASSCELLS: Those points are well taken. I noticed that only about 10 percent were smokers and an important issue, though, would be the weight loss. Weight loss typically follows a hospitalization. I know the important issue is the use of statens(?). That has gone up quickly and, as you know, statens save lives now and statens improve angina, beginning at about six weeks, according to Dr. Lance Goodall, based on PET scan data. Other studies it is more like six months but clearly the use of statens is very, very important and it is important to know whether there was a difference, whether the TMR group had more intensive medical therapy later. All we know is that a lot

of them stopped calcium antagonists and that may have saved their lives because we have got some doubt about those drugs.

So when you pool all that anti-angina drug data and say these patients are getting off their drugs, that is not very persuasive since all they are getting off for the most part is those calcium antagonists may have been killing them so let's not talk about that.

Let's talk about what they really are taking that may have helped them. We need to get that data and we need to see how they are dong on their cholesterol objectively and on their treadmill duration which is semi-objective and some things like that and don't forget I want to see that pacemaker and AICD data because those are important therapeutic options which may have accrued to your patient as a spin-off of the decision to have TMR. That is not an indictment of the procedure but it is important to know exactly what is causing the benefits here.

DR. BOYCE: Once again, I think those are very pertinent, excellent points. I can say that once again I can only comment on our experience at the Washington

Hospital Center. But all the patients in the trial, whether they were randomized to team or randomized to control, were taken care of at a tertiary level by one single cardiologist. So all of those patients were treated in an exact similar manner in terms of medications.

In terms of treadmill tests, although I don't have hard data to put up on the screen, one thing that we discussed at our own institution at length was it is remarkable how the treadmill time increased in these patients in terms of regardless of what the actual thallium showed, the amount of time that they are able to get on a treadmill and walk, really did increase dramatically at three TMR versus the follow-through.

DR. CASSCELLS: That is important. Now, how about this other issue of trying to keep these channels open? This issue has come up and I have read Dr. Frazier's assembled work on this and I am not sure what to make of it because I have got six or seven papers that have come into some of the journals I reviewed for recently and, of course, I cannot comment more than that except to say that they claim these channels in animal models don't stay open.

So one issue that I don't care if the mechanism is very much but an important issue is did your patients who get TMR get, did any of them get Ticklet, Diclopodine or cumadine or did they have a higher use of aspirin? Potentially beneficial interventions designed, for example, to keep a channel open but which might have had other benefits elsewhere.

DR. BOYCE: At our institution, and, once again, our institution, I did place the patients on cumidine but only for a three month period of time. They were not treated with Ticlid. Everyone for the most part, either the control group or the TMR group was on aspirin since once again nine out of ten of these folks had had at least one prior previous bypass operation.

DR. SWAIN: Let me just ask. I think I missed the cumadine part in here. What percentage of the patients with TMR had cumadine?

DR. BOYCE: All of them at this institution.

DR. SWAIN: But not all of them in the study.

DR. LEFEBVRE: No, that medical regimen was specific for each institution. I cannot tell you a

percentage. I would like to make a comment with respect to the number of AICDs and --

DR. SWAIN: In response to questions only.

DR. LEFEBVRE: Yes, in response to, right now we are looking at the exact number but it is very minimal, like something like two patients.

DR. LANSING: IN response to the cumadine, we have done 210 of these procedures. Forty percent of the patients were unstable. The ones who were unstable or pre-infarction got cumadine afterwards. The others did not and they all got aspirin sort of before and afterwards but the cumadine therapy was limited only to the unstable or pre-infarction group because we found there is a higher incidence of post-operative infarction in these critically ill patients so we are trying to prevent that.

DR. SWAIN: That is your group only. That was what the only question is what overall, there was no answer.

DR. LANSING: This is the biggest group by far so 40 percent of those.

DR. SWAIN: Do you have more questions?

DR. LEFEBVRE: With respect to some of the

questions you have asked, the study had an independent data safety monitoring board which looked at all adverse events and complications and they did not make any finding as to whether to stop the study or anything like that with respect to unwanted and undesired incidents.

DR. CASSCELLS: Would you follow up on the question Dr. Califf asked earlier? Did you and that data safety group come to an agreement as to when you would stop the study? As you well know, if you take multiple looks at the data as the data is accumulating, there is an understandable tendency to stop it when the therapy looks significantly beneficial. We obviously want to stop the study and offer that benefit to everyone who might be helped by it. But it is just as important to recognize that there are random walks in the data, the difference between the intervention group and the control group varies somewhat like noise and so typically confidence limits are drawn by the data safety and monitoring board and no one looks at the data and the study is not halted unless specific pre-determined endpoints across one of those, none of that was described in your PMA.

Can you comment on that?

DR. LAVIN: I think it is clear that they have not tried to stop the trial. Clearly if the angina results had been known earlier, they may well have stopped the trial on the grounds of overriding efficacy so it is clear that there appeared to be no rules that were in place to stop the trial for either efficacy or lack of efficacy.

DR. CASSCELLS: How was the decision made to stop the trial?

DR. LAVIN: It reached critical goals.

DR. CASSCELLS: Predetermined number of patients but you had 12 months follow-up designed for phase three and you have come to the FDA without 12 months data in phase three.

DR. LEFEBVRE: We have 12 months data from phase two and we saw phase three as a confirmation of the safety and efficacy findings of phase two.

DR. CASSCELLS: It looks though from the PMA like the trial stopped early so I am just wondering what those criteria were.

DR. LEFEBVRE: Actually, in the trial it is

ongoing. Patients are still being enrolled under a non-randomized fashion.

DR. SWAIN: Ron, do you have one last comment?

DR. WEINTRAUB: Yes, I was puzzled by that, too. There is a note that this, that enrollment of randomized patients was discontinued in September of 1996. Is that correct? And how did that decision come about? How was it made?

DR. SWAIN: Dr. Callahan?

DR. CALLAHAN: It was just reaching the target number of patients. The company wants to comment on the details of that.

DR. LAVIN: In my getting involved in this, I asked that very question. I think if you look in the original protocol for phase three, you will see that the sample size calculations allowed for 12 to 13 patients per group and because medical management was the control group, and there are a number of sites that are in the study, they were allowed to enroll 50 patients per group and then when they realized that there were difficulties with the completion of the SPECT data and the difficulties and the

people occasionally missing, they increased the sample size further to 100 per group in order to be able to have adequate power to be able to look at the primary endpoint which is the number of reversible defects and also to look at the other secondary endpoint which was the angina success rate of two or more improvement so that is my recollection of how the sample size was finally reached at the 200 total goal.

DR. WITTESS: That primary endpoint, was that at a specific time? Was it a 12 month endpoint? Was it a three month endpoint?

DR. LAVIN: From my review of the protocol, it appeared to be a global without any specific mention of time. That is why when we did our analysis of it, we looked at a longitudinal model that encompassed all post-baseline observations.

DR. SWAIN: Okay, well, we will reconvene at, let's say, 1:35 and see you back here.

(Whereupon, the meeting recessed for lunch at 12:22 p.m.)

A F T E R N O O N S E S S I O N [1:32 p.m.]

Agenda Item: Resume Open Committee Discussion

DR. SWAIN: Dr. Casscells had some specific questions, to get some answers. Why don't we go that into a limited amount of time of specific answers only with data.

DR. CASSCELLS: Thank you. Ward Casscells, Houston.

I had asked about patients lost to follow-up, in particular the lack of the symptoms and the lack of thallium tested; in some cases, the lack of all follow-up. I don't think you have anymore data, do you, than you did an hour ago on that?

DR. LEFEBVRE: No, we don't.

DR. CASSCELLS: Okay. I had also asked if you might be able to tabulate the patients' actual angina questionnaire, the Seattle or Rose questionnaire -- I think you used the Seattle questionnaire -- unfiltered by the nuclear medicine physician, who is not accustomed to making a diagnosis of angina pectoris. So, if you have that -- if we have the real data that the patient scored -- if you have that and if you are ready to present that, I would be

interested in hearing that.

Do you have that data?

DR. LEFEBVRE: We are not clear exactly what you are asking.

DR. CASSCELLS: I don't know how I can say it any differently. Angina pectoris is a symptom constellation based on the patient's symptoms, not the doctor's symptoms and generally -- and you state in your record that the patients all filled out a Seattle angina questionnaire. You subsequently state that the questionnaire was finally scored either by one of two doctors, half the time the nuclear medicine specialist and half the time the surgeon.

DR. LEFEBVRE: These are two separate statements. The Seattle angina questionnaire was used to assess quality of life. Angina pectoris was assessed by the physician and sometimes the nuclear cardiologist, but these were two different questions.

DR. LEFEBVRE: Okay. Well, it would be good, if you can, to pull up that data on the actual angina questionnaire.

DR. LEFEBVRE: The Seattle angina questionnaire,

you have seen the result as part of the quality of life findings earlier and they are also in the final pack.

With respect to angina, all the data that has been shown with respect to angina is -- has been assessed by the investigators or in some instances, nuclear cardiologists.

DR. CASSCELLS: I had asked you how it happened that patients had almost a complete resolution of angina pectoris but the number of defects only decreased from five to four. How are we to deal with the creation of patients who have four defects on scan that are now silent?

DR. LEFEBVRE: There is no data that has shown the linear relationship between the changes in angina pectoris and the changes in myocardial profusion. That is why the correlation that we use just tried to look at what was clinically significant changes in terms of angina pectoris, i.e., a decrease of two classes. And when you are looking --

DR. CASSCELLS: -- directional decrease -- excuse me. Go ahead and finish your statement.

DR. LEFEBVRE: And when looking at those clinically significant changes with respect to angina or

lack of clinically significant changes, then there was an agreement of 67 or 68 percent between the SPECT(?) data and the angina findings.

DR. CASSCELLS: That agreement is given in an ordinal scale, I suppose, because you have a 20 percent decrease in the number of segmental defects, but you have a 60 or so percent decrease in the angina symptoms. So, there is a dissonance there. You account for only a portion of the variance in your data and perhaps the statistician can speak to that.

DR. LAVIN: Philip Lavin.

I think that the thing that you want to keep sight of -- and this is something that is critical to the analysis of these data -- is that the SPECT data is not a gold standard for diagnosis of angina relief or angina degree. I don't think anyone in this room would call the SPECT a gold standard for it.

In particular, what we are doing is we are looking at the change in the score for SPECT for the number of reversible defects and we are looking at the change in the angina score. So, you have done a double disconnect. There

is no way in the world you would expect those data to be a hundred percent concordant. I think the fact that you see these data as 60, 70 percent concordant gives some credibility to the two, but they really are independent and not totally dependent endpoints.

That is why you ask for both the angina, you know, relief score -- that is why you also look at the SPECT. One does not totally, you know, displace the other. It is just good clinical practice that you look at both. We have correlation. That is all that I think one can reasonably expect.

SPONSOR: Dr. March would like to address that also.

DR. SWAIN: Do you want anybody else to address it?

DR. CASSCELLS: No. I appreciate that lesson in clinical medicine from the statistician. But I do practice it all the time and I am very familiar with the fact that the thallium score does not always agree with the symptoms. I think it is important to be as precise as one can be in accounting for soft endpoints, which leads to the point --

the other point I made is what other endpoints do you have. It is very important to know if the endpoints, particularly if they are not presented a priori, very clearly presented a priori, that they are not selected endpoints.

So, if you have treadmill test data, ejection fraction data, that kind of stuff is very helpful.

DR. SWAIN: Is that your question, what other endpoints are there?

DR. CASSCELLS: What other endpoints do you have? Any endpoints we haven't seen?

DR. LEFEBVRE: The protocol, the clinical protocol agreed upon by the FDA before the start of the study was very clear in the endpoints. The endpoints were going to be a change in angina. There were going to be a decreased resolution of an ischemia, as measured by SPECT. These were the --

DR. SWAIN: Excuse me. Can we just have concise answers. The answer of other endpoints, none. Correct. Okay. Is there another question you had -- let's try to finish up Dr. Casscell's questions.

DR. CASSCELLS: No. I think that is a good

answer. I didn't realize that the FDA had previously -- I have one more -- the FDA had previously preapproved that endpoint. That wasn't clear from the package.

I think the most important question is you may have -- the efficacy of this may be greater than you state or less, depending on what other therapies these patients received. I listed several therapies; for example, the use of cholesterol-lowering drugs, compliance with those drugs, aspirin, ticlophadine(?), warfarin(?), cardiac rehabilitation, cigarette smoking cessation and you did give me the information about pacemakers and AICDs, but you didn't give it to the whole group. So, you may want to restate that.

The whole host of therapies, which are sometimes -- sometimes differ between two groups on the basis of one group having been through surgery and having more exposure to the doctors and nurses.

DR. SWAIN: So, the AICD question?

DR. LEFEBVRE: There were six AICDs of pacemakers in Phase 2. There were none in Phase 3.

With respect to the change in medication, change

in medication was looked at to ensure that the relief of angina was not due to an increase in cardiactive medication. We looked separately at those three categories, nitrate, beta blockers and calcium channel blockers and you can see the result independently for the nitrates. It is an independent package.

I believe that Dr. Horvath would like to comment on the medication use.

DR. HORVATH: With regard to the medications, the purpose of the study was not to try to change the medications. It was to restart the medications as was stated postoperatively. There, therefore, was not an effort to specifically change medications.

There was no difference in the statin usage in either group, the treated group or the control group.

DR. SWAIN: What was the usage?

DR. HORVATH: The overall usage, I don't have that number, but there was no change as far as the other medications, aside from the calcium channel blockers, nitrates and beta blockers. That number is available.

DR. CASSCELLS: Excuse me. You mentioned warfarin

was used at your largest center in all of the patients who had TMR and then virtually -- in none or virtually none of the other patients. Did I misunderstand, Dr. Lansing? For three months there was a use of cumadin?

SPONSOR: That is incorrect.

DR. LANSING: I am sorry I am not up there, but --

DR. SWAIN: This is Dr. Lansing.

DR. LANSING: -- but I used them only in the unstable patients, not in the rest of them.

DR. SWAIN: How many patients had cumadin?

DR. LANSING: 80.

DR. HORVATH: Let me finish as far as the statins. The benefit of statins is relatively new --

DR. SWAIN: No, let's just go -- what percentage had statins and what didn't?

DR. HORVATH: Don't have that number.

Cumadin, the indications for cumadin, again, not with a percentage, were for unstable angina or if they were on cumadin preoperatively for appropriate conditions. There was not an increase in the use of cumadin as a result of having this treatment.

DR. SWAIN: Do you have the numbers of who had and who hadn't?

DR. HORVATH: No.

DR. SWAIN: Not that there was a change. Okay.

DR. CASSCELLS: What happened to their cholesterols, their weight, their glucose? Do you know any of that, by any chance?

DR. HORVATH: The cholesterols and glucoses were not followed specifically. The weights are obtainable. We don't have the data at present, but the weights are, obviously, obtainable from the nuclear medicine scan. When they had those scans done, their weights were taken.

DR. CASSCELLS: Finally, you mentioned when you were last up at the podium there that your ultrasound data suggested channel patency and that your ultrasound data had a resolution of 1 micron. Did I misunderstand?

DR. HORVATH: No, I think the 1 micron was from the questioner. It is 1 millimeter and that is the size of the channel. I apologize if that was the impression.

As far as the papers that you quoted, there are equal number of papers that are published that show patency

versus non-patency. There is a wide variety of animals being employed in those studies. There is a wide variety of lasers being employed in those studies and most of them are not in the setting of chronic ischemia.

DR. SWAIN: Okay. Dr. Sethi.

DR. SETHI: Thank you.

I just wonder why did you change the definition of "angina" or classification of angina, you know, when you have got a standard, accepted, Canadian classification of angina. You changed that in your Phase 2 study and then you changed it again in Phase 3 study. It is very hard to compare and especially in the future if we are going to compare other studies with this study.

Any rationale behind that?

DR. LEFEBVRE: We actually did not change the classification of angina between Phase 2 and Phase 3. The case report -- the wording on the case report form may have been somewhat different, but it was the same classification that was used between Phase 2 and Phase 3.

As far as the other modification, which was the addition of no angina, that was just to characterize those

patients who had no angina. Class 1 characterizes patients who have angina. If somebody has no angina, we needed to come up with a classification that did not have any angina. So, that is why we added Class 0 to the typical Class 1, 2, 3, 4. And they were exactly the same for Phase 2 and Phase 3.

DR. SETHI: The reason I say that, you know, the more steps you have, the more changes -- the more possibility of seeing changes. If you have four classes, then changes will be rather marked changes or if you go to 5, 6, 7, 8 steps. I think you have to be careful about changing the well-accepted classification of angina unless you can validate with other rates.

DR. LEFEBVRE: You are correct, but if you would like to take the other approach, you could combine the Class 0 patients with the Class 1. That would not affect the success rate with respect to angina. And as shown in the presentation earlier, 50 percent of the patient, following TMR, had either no angina or Class 1. So, if you put them all in Class 1, you would end up with 50 percent of the TMR patients following the surgery with Class 1 angina.

DR. SETHI: The question had been asked earlier about whether you did get any CPKMB based on -- combined perioperatively. The answer which I heard was that in Phase 2 you did, but did you collect any data in Phase 3?

DR. LEFEBVRE: The study did not require for the collection of any sort of CPKMB fraction. We can have other investigators comment as to if or not they have done such measurements. We did not do it and there was no study published.

DR. HORVATH: As an individual institution, we followed CK and MB postoperatively and did see an obvious CK rise, did not see a significant MB rise or an increase in MB index, unless they also had evidence of a myocardial infarction based on EKG clinical pictures.

DR. SETHI: The next question is about your follow-up, which has been mentioned by everyone. It appears that at six months, they are missing 33 percent of the patients who have low assessment of angina. When you come down to one year, there are a very small number of patients. There are only, I think, 15 patients in each group.

Are those number good enough to make conclusion

that TMR is better than the controls?

DR. LEFEBVRE: I would respond in two ways. First of all, there was a statistically significant difference between the two groups at 12 months. Second, although the sample sizes in Phase 3 are small, do not forget that Phase 3 was a confirmation of the Phase 2 safety and efficacy findings for which we have 132 patients at 12 months.

DR. SETHI: Well, unfortunately, I would like to look at the controlled trials as definitive trials. You know, Phase 2 trial is okay. It is going to show something, but Phase 3 trial is a trial which I like to put all my money on because there is a trial ready to be randomized. There is less possibility of bias as you can see from some other SPECT data.

So, I like to pay more attention to the Phase 3 studies only at this point.

DR. LEFEBVRE: Phase 3 demonstrated a statistically significant difference between the angina and between TMR and control group and Dr. Boyce would like to comment on the Phase 3 results.

DR. BOYCE: I would just like to mention that when

we looked at this data and discussed it with various members at the FDA, et cetera, I certainly made the point that from a clinical standpoint, we -- this is not a drug trial. This isn't a Phase 2 and Phase 3 type of way of thinking with a drug trial. This is a device.

When you look at these patients, it is really -- in my mind, we look at the entire cohort, the randomized and the non-randomized. If you do that, you essentially have 300 patients that receive TMR and 100 that acted as a control. So, that would help you interpret the data a little bit better and maybe not look at the fallout in some of the data in the same light. Because, in essence, there is no difference in the entrance criteria.

It was strictly a matter of when that individual presented to be treated. If they presented a year prior, they would have been in the non-randomized arm and in the following year, they would have been in the randomized arm. It is not as if we changed the entrance criteria. So, Patient 82 in, quote, unquote, Phase 2 -- and I really take issue with the terminology. In the non-randomized, Patient 82 in non-randomized should have exact same patient

criteria, was treated the exact same way as Patient 82 in, quote, unquote, the Phase 3 or, more appropriately, the randomized trial.

So, I think it is very important for the committee to look at all the data in toto and realize that what we are really looking at is a patient population of 400, with 100 being controlled and 300 being treated.

DR. SETHI: It is pretty hard to convince me that -- you are comparing apples with oranges.

Another question is how did this procedure differ from the old Vineberg(?) procedure?

DR. LEFEBVRE: It is a totally different concept, totally different technique. I would say the two procedures have nothing in common.

And Dr. Frazier would like to comment.

DR. FRAZIER: Well, I think there is, of course, no correlation with the Vineberg except for the principle -- the Vineberg's success was related to this sinusoidal(?) circulation. Other than that, I can't think of -- the Vineberg was just a burrowing of the internal mammary artery directly into the myocardium with open vessels.

This is a procedure designed to affect profusion in the endocardial layers with the use of a laser. It is more akin to what Sim(?) reported, I suppose. That would be a more germane comparison except Sim did not have the technology in the fifties that this technology represents and, of course, as you know, he reported improvement in his -- both experimental model and clinically, free coronary bypass.

So, I mean, this is just an elaboration, I think, and an improvement as regards the technology.

DR. SETHI: You are talking about the mode of actions or how does it work. Old Vineberg procedure does the same thing, you know. You make a big hole in the heart and the blood vessels, you know, the bleeding from the artery joins the sinusoids and into the blood flow.

DR. FRAZIER: Well, I think from that principle it is just the blood is coming from a different way and it is a different mechanism. So, I think to equate it -- and, of course, there is -- as I said earlier, I am not -- I think this question of mechanism of action is something that is going to remain to be identified.

My concern initially was demonstrating by the best technique available, that there was improved profusion, which we have done.

DR. SETHI: Let me give you some follow-up I did on mine and published in 1973 and at ten year follow-up, there was a 50 percent symptomatic improvement in patients in angina and the remaining patients about 30 to 35 percent said that they feel good and only very small number of patients were worse at ten year follow-up.

So, what I am trying to say is that the angina itself is very hard to say that this device decreases angina compared to control based on some older studies.

DR. FRAZIER: I don't understand. You can only do them through a blinded study, which is what this was. This was a randomized, blinded study with angina and thallium scan, approved by the FDA as a follow-up. How else can you do it? You can do the PET scan, but nobody can afford that. We would have liked to do it.

Now, as far as the studies of, you know, these Vineberg studies, the bulk of our patients had patent mammary grafts, direct patent mammary graphs and they still

had angina. That is the bulk of the patients we treated had a patent mammary graft. The problem is a mammary just doesn't supply enough blood in most patients, even when it goes directly -- or in many patients even when it goes directly to the artery and is patent to control their angina.

DR. SETHI: But what I am saying is this could be all placebo effect.

DR. FRAZIER: Well, of course not. That is the reason you randomize the study.

DR. LEFEBVRE: We would like Dr. Lavin to address that placebo effect.

DR. SWAIN: Do you have a specific question regarding placebo effect?

DR. SETHI: Yes. Let me go one step further here.

What time did you collect your SS36 data, at what point?

DR. FRAZIER: You asked about placebo, didn't you?

DR. SWAIN: No, no, he hasn't asked about that.

DR. FRAZIER: What about placebo effect?

DR. SWAIN: Hang on, hang on, guys.

DR. SETHI: I will come back on that.

DR. SWAIN: If we have a specific question about placebo effect, it will be asked. Okay?

DR. SETHI: At what time did you collect your SS36 data?

DR. LEFEBVRE: The data was collected at baseline, three months, six months and twelve months.

DR. SETHI: Suppose a patient came to your institution, was it collected before randomization or after randomization?

DR. LEFEBVRE: I would say I don't have the answer right now, but what I can tell is that there was no statistically significant difference between the control group or TMR group at baseline with respect to any of the quality of life parameters. If the treatment assignment had, indeed, biased the patient, you would have had a statistically significant difference between the scores of the two treatment groups.

DR. SETHI: So, you don't know when the data was collected?

DR. LEFEBVRE: It is center to center dependent.

DR. SWAIN: Okay. Next question.

DR. SETHI: I would like to get a little bit on the autopsy data. How many total deaths have you had in the whole group, your number of deaths?

DR. LEFEBVRE: In Phase 3 we had --

DR. SETHI: All the patients, autopsy data -- what I am trying to get at is to look at the number -- how many patients have channels which are open at autopsy? If my numbers are correct, there were 16 patients who had autopsy done and going through each autopsy -- none of the channels were open and one heart -- in three autopsy reports, there was no mention of any channels. So, I presume they were closed.

DR. LEFEBVRE: Well, actually, they may not have looked at them.

DR. SETHI: A randomized study with a foreign device you are talking about and, you know, is it the centers --

DR. LEFEBVRE: The problem is when the patient died at follow-up, the patient was very often living far away from the investigational center. As a result, that

patient may have gone to the local hospital, died and had an autopsy there. By the time the investigator found out about the death, it was too late to request a specific histological examination.

DR. SETHI: In eight patients, there were no channels open. This was specifically mentioned by the pathologist. In three patients, I can't figure out what happened there.

My specific question is the patient --

DR. LEFEBVRE: Actually, the channels were filled. They were not -- which is different from closed.

DR. SETHI: My specific question is about the patient with the heart transplant. What was the pathology in that patient? I can't figure it out.

DR. LEFEBVRE: Actually, there was one patient that we did from Texas Heart Institute, who had an autopsy -- I mean, the patient had a heart transplant and the old heart was looked at. We can talk about it, but I believe they found channels. Dr. Frazier. Excuse me.

DR. SWAIN: Do you have a further question about that?

DR. SETHI: Were channels open on that heart?

DR. FRAZIER: Yes.

DR. SETHI: And the patient is still having significant angina?

DR. FRAZIER: No. He wasn't having angina to start with. He was having -- that is an entirely different study. It is not germane to this presentation at all. We have been studying patients suffering from advanced impairment of the myocardial function due to the severe generalized coronary atherosclerosis in the heart transplant patients.

We have two such patients, one of which died of unrelated causes three months after the procedure when we studied that.

DR. SETHI: No, no, no, no. One of the patients in this -- in your protocol -- in this cohabitations underwent heart transplant.

DR. FRAZIER: Underwent a heart transplant --

DR. SETHI: After one of the subsequent procedures.

DR. FRAZIER: Well, I can't address that. I

thought you meant the --

DR. SWAIN: You can turn that slide off.

May we have the lights back on.

Dr. Sethi, further questions?

DR. SETHI: I will come back.

DR. SWAIN: Dr. Ferguson.

DR. FERGUSON: Dr. Ferguson in St. Louis.

I am impressed with the way in which this procedure treats patients that have no options or alternatives left to them. I think in that way we need to keep a balance when we talk about it.

One of the reasons that I think we are having difficulty or I have had difficulty with this procedure and the concept of it is that we don't know what the etiology is. We talk about channels. We are not sure that channels are the problem.

I personally don't think that the etiology is that important unless the etiology is due to something that can ultimately make the patient worse and this gets around to my specific question. That is, what evidence is there that these channels are not denervating the heart to the degree

that angina is improved?

DR. LEFEBVRE: I would like to state that the only study which was published regarding denervation was conducted in an animal model, with a different type of laser. It was produced as an abstract form and has not been yet published in a peer reviewed journal. However, Dr. Horvath would like to comment on the findings.

DR. HORVATH: I agree that the mechanism is probably not what we are going to solve today and you bring up denervation as a possible mechanism and an elegant study, in fact, from your institution looked at that as was mentioned in an animal model. In that experiment, they detected a decrease in blood pressure as evidence of denervation when the animal was stressed. We have not seen that clinically.

Likewise, the volume of tissue that is ablated, if you take the scenario where the patient had the largest number of holes drilled per the size of the left ventricle, it is less than .05 percent on the left ventricular mass. You have to then assume that these holes are incredibly specific, maybe even better than most catheter ablations in

the EP lab are able to do as far as completely deenervating the heart.

I agree that if denervation, while it may play a role potentially at least in thinking about it, it sounds that it would be harmful. If it was, in fact, harmful, then I think you would see that there is an increase in deaths, an increase in MIs, an increase in unstable angina and you wouldn't see improved quality of life, particularly if you are comparing it to the control group, which was not the case.

DR. LEFEBVRE: Dr. Lansing would like to make one additional comment, a complementary comment.

DR. SWAIN: Okay. Do you have data about denervation? The question is data about denervation.

DR. LANSING: I have evidence against denervation, yes, and I want to show you some of the case reports, cases from our hospital. From this you can make your own conclusions or deductions about the possibility. I think this is very beneficial.

Could I have the first slide, please? I have about six slides and I will be very brief.

First of all, we have the fact that post-op thallium in institution did in over half the cases show an improvement and in only six was it worse.

Cardiac medications in over half the patients who went down --

DR. SWAIN: Excuse me. Can we have denervation data?

DR. LANSING: It is coming. Next slide.

DR. SWAIN: Okay. So, let's skip to the slide that has the denervation.

DR. LANSING: All right. Next slide, please.

DR. SWAIN: We have really got to get on track.

DR. LANSING: Here it is. This is the only slide like it in the world. This is three months, six months, twelve months. Blue is no angina. The red is one. The orange is Class 2, Class 3 and Class 4. Now, you notice that at six months it is better than three months. At a year it is better than six months, a progressive improvement.

If this were denervation, it ought to occur immediately. It doesn't. It is a progressive thing. So,

this suggests that there is an ongoing process here, not something that is specific, bang -- we don't denervate the right ventricle or the septum.

DR. WITTES: Can I ask a question about that slide?

Do you have data on the same patients. The twelve month data, do you have a subset that --

DR. LANSING: Some of the six month are the ones that are twelve. Obviously, at three months, I don't have them on the twelve month --

DR. WITTES: No, no, no. That is not what I am asking. You are pointing to an improvement, but I am asking whether if you took the subset that had all three observations, would you see that same improvement?

DR. LANSING: Yes.

DR. WITTES: You have those data?

DR. LANSING: Yes.

DR. SWAIN: The pair T tests, the patient who was her own control, is it statistically significant that there is improvement?

DR. LANSING: I have not done the pair T test. It

has been four years since I did any good statistics, but I think this is a very important picture and, again, this is only to make you think. It is not proof. I admit it.

Next slide, please.

DR. SWAIN: Excuse me. Hang on. Dr. Califf.

DR. CALIFF: I just want to make the point that even the parent data is not enough because one way that the percentages can shift is if people are dead in the second category. That has been well described in heart failure studies. The treatments that lead to high immortality end up with better functional status because the sick patients have died off when you get to your follow-up.

So, it is a complicated issue that you need to really --

DR. LEFEBVRE: We actually can answer that very specific question after Dr. Lansing finishes his point.

DR. LANSING: Would you agree that denervation is unlikely under this -- if this picture is true?

DR. SWAIN: I don't believe I have enough data to say that.

PARTICIPANT: The only thing that changes is Class

0.

DR. LANSING: That is right. But the whole shift is that way.

Next slide.

DR. SWAIN: Excuse me. Dr. Ferguson, do you have --

DR. LANSING: Along the same line --

DR. SWAIN: This is an answer to your -- excuse me a second, Dr. Lansing.

DR. LANSING: Sorry.

DR. SWAIN: Do you have further questions about denervation that Dr. Lansing can help you with?

DR. FERGUSON: I do not, no.

DR. SWAIN: Okay. Thank you.

DR. LANSING: Not only was there progression improvement --

DR. SWAIN: Hang on. I think we have finished answering Dr. Ferguson's questions about that and if there are further questions from panel reviewers --

DR. FERGUSON: I am not quite through. One other question of the group and that is that on several occasions

I have heard some of the speakers say in our institution, at least, it was done this way or in our cohort of patients we did this.

I would like to be assured that there was some overall regulation of the protocol here so that when we talk about the 13 or 14, whatever it was, institutions, say, just exclusively in the Phase 3, that they were all treated in the same way and that the cardiologists were asked to do the same things and so forth.

DR. LEFEBVRE: I can answer that question.

It is correct that the protocol did not describe in detail what sort of, for example, cardiac medication were to be given to the patient. However, there was a strict protocol that had to be followed that specifically told the science what they had to do, what sort of follow-up they had to do, what type of test they had to do at each follow-up.

Furthermore, to confirm that there was no site-to-site variation, at baseline, and the patient characteristics of all patients were compared and there was no difference among the treatment sites and also to make sure that there was no variation within the TMR outcome, the angina results

were looked at independently for all of the different sites and there was no statistical difference between the angina outcome of the clinical sites.

So, even though there was no specific requirements as far as cardiac medications, for example, the global outcome was similar at all sites participating in the study.

DR. CERQUERIA: I would like to reiterate some of the things that Dr. Califf said this morning in terms of the data dropout for the thallium. I have been involved in these types of studies for over 14 years and when you are only looking at 32 percent Phase 2 and 44 percent of the patients in Phase 3, it is a stretch to conclude that there is a difference in the profusion defects between the two groups.

I know you tried to do an analysis to see if there were group differences, but there were differences; things like medications. You have shown in terms of patients who got the procedure were on fewer medications. I think with this kind of a dropout, it is very difficult to make definitive conclusions on the basis of the profusion information. That is a statement.

I have some other questions about the actual methodology of the profusion studies. Was there any sort of quality control performed on the equipment used at the sites to make certain that they were accurate in measuring defects? Was the equipment standardized in any way? Were phantoms sent out?

DR. LEFEBVRE: No phantoms were sent out, but our protocol specified exactly what were the tests that had to be done.

DR. CERQUERIA: Okay. Was there any quality control done on the cameras in terms of routine things that can be done to check the performance of the equipment?

DR. LEFEBVRE: These tests are clinical tests that are done on a regular basis by the hospital. There was nothing really special about them. So, there was no specific test done.

DR. CERQUERIA: But I can tell you -- and I have been involved in studies myself and I know that other studies involving, you know, 40 and 50 separate centers, you can actually send a phantom out to see the size, the resolution of the nuclear equipment to see how well -- how

small a defect can be analyzed.

So, I think that is a definite limitation.

Do you know what the compliance was with -- for the Phase 2, there was no standardization. People could have had an exercise thallium. They could have had a pharmacologic thallium. In Phase 2, you -- it was a diputamal(?) with the reinjection, which I think is a very good protocol, but do you know the compliance of the data that you have available? How many people actually followed that protocol?

DR. LEFEBVRE: We are looking at the data. We can give you the exact percentage.

DR. CERQUERIA: Because if some people were doing exercise, which I think was indicated --

DR. LEFEBVRE: No. In Phase 2, indeed, as you mention, there was no specific requirement. In Phase 3, we -- because of the fact that the patients could not undergo thallium tests -- excuse me -- exercise testing, we specifically went to a chemical stressing method to make sure that the stressing would be similar at baseline and at follow-up.

DR. CERQUERIA: Okay. Now, you are using sort of a semi-quantitative method, where you are taking probably far too many segments of the ventricle to break it up into a reproducible method and you really have not shown that your method of the analysis was reproducible in terms of inter and intra-observer variability.

DR. LEFEBVRE: Actually, that goes back to a comment which I believe Dr. Califf made earlier. The methodology that we use was validated and Dr. Mannting can explain exactly how the tests were analyzed and why they were analyzed that way.

DR. CERQUERIA: Okay. You know, briefly, I -- he basically gave me some additional information, which I understand was incorrect in the form, but what is the reproducibility, the inter and intra-observer reproducibility?

DR. MANNTING: Dr. Mannting, Brigham & Women's Hospital in Boston.

The method used for reading these profusion images is the clinical basic method of doing it. Dividing the myocardium in segments like this, the reproducibility is

plus/minus two segments.

DR. CERQUERIA: So, in your particular laboratory -- okay. Well, that is worthwhile data to know.

Now, there are ways of doing quantitative analysis, which, again, gives you better reproducibility in some cases. Is there a reason that you didn't do a quantitative method of analysis?

DR. MANNTING: Would you answer that?

DR. LEFEBVRE: When the protocol was designed we did not -- we decided not to use quantified analysis. Now, if it was to be done today, I would say that we would definitely have chosen that approach. Additionally, the data that was processed by the core lab is still available. So, we will go back to try to get the quantified analysis.

DR. CERQUERIA: Well, that doesn't deal with the problem with the data that you didn't acquire studies on, but at least with the data that you have, it would make it more reproducible. I think that would be very worthwhile to do.

The other thing that I am sort of struck by also is that if you look at the defect size on these patients,

both in terms of the fixed defects, which would be with old infarcts, and the amount of reversible ischemia, most of these people had about 12 1/2 of the 24 segments that were abnormal, with maybe eight or nine of them being infarcted. And, yet, your rejection fractions on these patients were like 47 percent in Phase 2 and 50 percent in the Phase 3 study, which is a little bit -- I don't quite understand why people with a third of their ventricle infarcted would have such normal rejection fractions.

DR. MANNTING: There are fixed defects and there are fixed defects. Some of the fixed defects represent the soft intracardial MI. Some of them are transmural(?). You wouldn't expect patients with mainly non-transmural defects to have that affected. I think that is one of the explanations.

DR. CERQUERIA: Perhaps, but still if a third of the ventricle doesn't -- and it is possible that some of that is hybrinating, but if that is the case, then you would have expected the method of creating improved blood supply to have improved the fixed profusion defects and you show that there was no change in the fixed profusion defects in

the TMR patients. Is that correct?

DR. MANNTING: I didn't get the question.

DR. CERQUERIA: All right. Fixed defects -- and thallium is not a perfect marker. There are some areas that are severely ischemic but are viable and if your method actually improved blood flow, you would have expected some improvement in profusion in the fixed defects, but your data for both Phase 2 and Phase 3 did not show any improvement.

DR. MANNTING: The scorings were not quantified. It was a "yes/no" situation. I don't know if the segment had a normal resting profusion or not and I don't know if the segment had ischemic changes or not. So, we didn't look for changes in abnormality. That is where quantification would have been helpful.

DR. CERQUERIA: Okay. So, that is a serious limitation. But I am still struck by this EF difference.

DR. MANNTING: Oh, yes. Where did we get the 40 percent from? Is that from the protocol?

DR. LEFEBVRE: Excuse me. I missed that part --

DR. CERQUERIA: The ejection fractions, if you look at the summary of clinical studies that was performed

on Phase 3, the ejection fraction was 47 percent. It ranged from 15 to 77 into Phase 2 and then for the Phase 3, the ejection fraction was, again, 50 percent and for the TMR it was 50 percent in the controls.

DR. LEFEBVRE: That was correct.

DR. CERQUERIA: Yes. Which is still a very high ejection fraction in patients who have had a lot of damage.

You have brought up the PET data several times, which, again, was from a single center. Sixteen patients were done. You showed data on about eight of them. I am just not certain you can do very much with the PET data. It is intriguing, but I don't think you can really reach any conclusions on that basis.

DR. MANNTING: I agree.

DR. CERQUERIA: Now, getting back to the Phase 2 trial, in one of the summary data sheets that was put together, there was an actual improvement, not just in the segments where you created the holes with the laser, that if you looked at the total ventricle, there was an actual improvement in profusion. It was like 1.7. If you looked just at the free wall, where you actually did the laser

treatment and it was 2.2 when you looked at the whole ventricle, which means, at least, you know, half the segment showed improvement, which would suggest that your effect was very non-specific.

That was not borne out in Phase 3.

DR. MANNTING: That would be a correct interpretation.

DR. CERQUERIA: But do you think that is a limitation of the scoring method or do you think this thing is doing miraculous work on other parts of the heart?

DR. MANNTING: I think it is a limitation of the scoring and there are limits for how detailed conclusions you can draw from the scoring of this type.

DR. CERQUERIA: Okay.

DR. LEFEBVRE: It was also, indeed, the way that the channels are created. Some of the channels may have been created in the near vicinity of the septum and those channels could have through whatever mechanism -- we are not saying -- you know, it could be direct or indirect profusion but that could have affected the profusion in the septum.

DR. CERQUERIA: Or it could be a limitation of the

measurement technique, which is relatively inaccurate.

Okay. Those are the major question I had.

DR. LEFEBVRE: You had asked a question. Seventy-six percent of the protocol were done exactly -- excuse me -- 76 percent of the studies of the Phase 3 with the protocol.

DR. CERQUERIA: Seventy-six percent of the 44 percent that you have complete data --

DR. LEFEBVRE: No, no, no, no, no. Seventy-six percent of all the studies. The 44 percent were all done -- met all of the study requirements.

DR. CERQUERIA: Right. But you can't look at all the other data. So --

DR. LEFEBVRE: We saw this morning as to why we have the attrition rate. There were a few losses at each of the different steps.

DR. CERQUERIA: No, I realize that, but if you are going to choose that as an endpoint, you have to basically accept the fact that there is going to be a dropout and you really need to come up with an endpoint where you can achieve -- you know, the TIMI(?) trials had at least 70 or

80 percent of all the nuclear data that was gathered.

So, if you could only do 32 percent in Phase 2 and 44 percent in Phase 3, you have an unrealistic endpoint. Do you need all those time intervals?

DR. LEFEBVRE: Actually, I would say that it is not an unrealistic endpoint. It is just that we should have realized up front that we were going to have such an attrition rate and compensated for it in the design of the sample sized. So, instead of having to go from a sample size of 100 to a sample size of 200, we would have said -- had we known, we would have said up front we expect an attrition rate of x percent and because of that, we would like to enroll that many more patients to compensate for those losses.

DR. CERQUERIA: Yes. I wouldn't accept that. I am sure the statistician would have a problem because you are still going to have the same problem of selecting of which patients dropped out. I don't think that would really answer the question. I think you need to, perhaps, you know, decide that you want endpoints at six months or twelve months, where you are not going to have all those missing

data sets and try hard.

I mean, you know, people do 40,000 patient studies internationally and you are trying to basically get data on 200 patients, where you really need to get that information.

I have no further questions.

DR. SWAIN: Okay. Let me just comment that Dr. Larry Friedman from NIH has joined our panel for this afternoon and the next questions will be Dr. Weintraub.

DR. WEINTRAUB: I will try to be fairly brief. Just a couple of -- just one statement first.

Having been on the panel for awhile, I greatly appreciated the book. For those who have been around for awhile, we used to get three feet of data and now we get one little tiny book. And it was a pleasure to go through. I think the staff, FDA staff, are to be congratulated.

Also, the other thing is that the sponsors have presented a randomized study. It has problems, but I think the message is finally getting out that the proper studies have to be done in order to seek approval.

Having said that, the first question I am going to ask is really not so much to the sponsors, but really to Dr.

Dawson and Dr. Wittes. I am on the horns of a dilemma here because a lot of my thought processes relate to the things that other people have brought up. That is, what does one -- how does one handle the missing data? Is the amount of missing data appropriate or inappropriate? Can we assess the device, realizing that this is a clinical study, that there are lots of difficult problems obtaining these data, can we assess it properly, considering that, for instance, for the radionuclide studies we only got 42 or 44 percent, depending on how you -- whether you add the 10 extra cases?

Are the reasons for the dropout of the studies legitimate? And can an evaluation be made without it?

In looking at the radionuclide study, it seems to me that we need a little bit more detail. If you look on page 94 -- I think I have all these right -- I would like a little bit more explanation of what -- I am not addressing this so much to the sponsors as to our own in-house experts.

The non-preventable losses, are they truly non-preventable? And, again, the question is can we assess this appropriately from the data given? Or going back to page 63, the angina assessment, there are 13 missing in the first

three months of assessment. This is intent to treat group of the controls, the control intent to treat group. There are 13 missing.

Now, were those 13 missing because they haven't matured? They were late to come into the -- or they were late additions to the cohort? Or are those data just missing because they are not there?

DR. LEFEBVRE: Most likely it was due to the fact that the data had not been received yet by PLC.

Excuse me. Exactly when looking at that chart, you have to keep in mind that some of the patients died. So, those, obviously --

DR. WEINTRAUB: No, no, but those are accounted for on the right hand side. It says four deaths lost to study 1, but there are still 13 that have got no assessment. Now, there is no angina assessment in 13 out of 101. You know, why?

DR. LEFEBVRE: Obviously, we wish we had that data. We do not have it. Now, whether we don't have it because the patient just didn't come back for the follow-up, because the data was late in coming from the sites to the

sponsor. I think that that is -- that doesn't change the fact that the percentage is there.

What needs to be seen when looking at the potential impact of those maybe not perfect compliance records, you have to look at the correlation between Phase 2 and Phase 3. In Phase 2, we had 90 percent -- we had a 90 percent compliance. In Phase 3, we had a compliance lower than 90 percent, but the results are exactly the same.

DR. WEINTRAUB: On page 431, on the comparisons of symptoms and thallium scans, again, going back to -- well, I will take that separately. Let me ask the statisticians -- and we are sort of beating on this, but I really sort of need a little guidance in terms of what I can accept as statistically legitimate.

DR. WITTES: Let me try. And actually I think that my view is probably a little different from Dr. Dawson's because I would have shaded the words differently.

It seems to me that what we have here is several different kinds of missing data that we are conflating. We have data missing for reasons like death. I mean, you can't get angina because the person's dead.

Then we have data missing because the protocol specified that under certain conditions, like you had another procedure, you weren't going to get your angina mentioned. Now, I have trouble with that. I have a lot of problems with that. I would like to have seen the angina measured.

Then we have missing data because it is administratively missing. We don't have 12 month data because the person hasn't reached 12 months. That is a qualitatively different thing, but that raises a question that was addressed before. What was the stopping rule for this study? Why did it stop -- when the data were unblind, why did the study stop without a prespecified time rule?

Now, is there a definite -- and the other question that I had as I was reading this is given the Phase 2 results, it seems to me what the Phase 2 results said was that it had to be -- if either SPECT or angina was to be used as an endpoint, there had to be extraordinary efforts to get the endpoint because that is what the -- one of the messages of the Phase 2 study was for me, that these were difficult endpoints to get hold of.

Yet, I didn't see in the discussion of the protocol or the discussion of how the primary endpoint was going to be measured any way of accounting in a rigorous way for -- you know, you enter the trial and, therefore, you declare yourself in the trial and how are you going to measure that at the end?

I find this kind of missing -- this amount of missing data very problematic, but I am also more worried or at least as worried about something I alluded to before, the possibility that there is this differential follow-up. If I am interpreting -- let me go to page 119, which to me is very worrisome. Page 119 is the incidence of AMI, is the Kaplan-Myer estimator in the Phase 3 study.

Now, what would expect -- and we know that the mortality rates are very, very similar in these two groups -- so, what one would expect -- again, unless I am reading this wrong -- is that you would see the same amount of dropout in the TMR and in the control group over time, suggesting that, well, maybe it is just a random thing and people don't show up. But what we see is at six months, by six months there is a much larger dropout in the control

group than the TMR group.

DR. LEFEBVRE: Could we answer?

DR. WITTES: Yes.

DR. LEFEBVRE: The reason why they -- it is not a dropout. It is just that the control group, some of the control group patients crossed over. And as a result, they were just lost to study. It is just that those patients drop -- excuse me -- crossed over and, therefore, they were in another arm of the study.

DR. SWAIN: But that CNO-X is the non-crossover, right?

DR. LEFEBVRE: That is correct.

DR. SWAIN: So, that has dropouts, she is asking.

DR. WITTES: No, no. I said the 47, you extracted from those, the crossovers?

DR. LEFEBVRE: That is correct. The 47 corresponds to those patients who at no point of the study crossed over; that is, those patients who remained on medical management for the entire duration of the study.

DR. WITTES: So, where is the Kaplan-Myer curve that shows the intent to treat group?

DR. LEFEBVRE: The intent to treat group is -- it is not -- the curve that is shown here -- you have three curves. One is the TMR group. One is the control without any crossover and the group in the middle includes those control patients up to the point of crossover.

The data is not shown for the intent to treat.

Do we have the opportunity to answer some of the questions that you have raised? You listed five or six questions and we would like to have the opportunity to answer to them.

DR. SWAIN: We are doing this by proxy.

DR. WEINTRAUB: That is fine by me. I mean, I am deferring to the statisticians.

DR. SWAIN: What questions do you want answered from the company?

DR. LEFEBVRE: I mean, I took a list.

The first one is I am sort of curious as to under what condition of the protocol were angina not supposed to be assessed. You made the statement saying that there was a condition stated in the protocol under which angina was not to be assessed.

DR. WITTES: I understood it if somebody had another procedure.

DR. LEFEBVRE: If somebody got another procedure, they were censored from and dropped totally from the study. That is correct. But as we have shown earlier today we are looking -- we are including those additional procedures as failures that did not change the success rate.

DR. WITTES: Yes, but I think we can't separate the angina from the imaging. The imaging, as I read it, was the primary endpoint. So, I am very comfortable with the analysis that says even though everybody -- even if you throw everybody into the worst arm, you are going to see, in fact, an answer. I mean, I think that is abundantly clear.

I don't think it is so clear with the imaging.

DR. LEFEBVRE: Actually, when you look at a different sort of analysis that were conducted, TMR versus control group, TMR versus control without crossover and TMR versus intent to treat and you are looking at it from a SPECT fusion standpoint, there was differences or in the worse case, in terms of the intent to treat, there was still a very significant trend with respect to the differences

between TMR patients and control patients -- and control group.

DR. WEINTRAUB: I was sort of going to ask that in a somewhat different question -- a different form. If you look at page 431, what happens if you take the lower right hand box and call all of those failures, just for fun? In other words, let's say that if the scans are worse -- no matter what the symptoms are, the scans are worse, then we are going to call that a failure.

If they are the same or better, we are going to call it a success. How does that pan out?

DR. LEFEBVRE: With respect to?

DR. WEINTRAUB: With respect to one of the control groups. I mean, the control groups, it is pretty clear --

DR. LEFEBVRE: I think you can just turn the page and look into page 432. You can see that for the control population, the SPECT data clearly indicated that most of -- there was only one -- there were two control patients that had an improvement in SPECT data and at six month , there was only one and that patient also had improvement in angina.

I mean, I think it is clear that when you look at it -- and this is -- obviously, we cannot give percentages because I don't count that fast, but --

DR. LAVIN: I just did. It is over 50 percent -- Phil Lavin here -- it is over 50 percent for both three months and six months in the bottom left corner as opposed to 5 or 10 percent for a control in the bottom left corner. So, by that measure, you have statistical significance.

DR. EDMUNDS: May I say something?

I first raised this particular figure and for me, and I asked you to answer the question -- I am not really sure that I got it over to you correctly so that you could, but I would have to say that the lower figure, the one stated on page 431 -- and perhaps you may want to comment -- shows that there is no concordance between the relief of angina and the profusion of the myocardia. There is no concordance.

In a way, Dr. Casscells got to the same thing via the fixed defects. You have the fixed defects reduced by 20 percent -- the reversible defects reduced by 20 percent, but the angina reduced by 70 percent. But this figure to me,

unless someone can teach me how to read it properly, says that there is no concordance between the relief of angina and profusion of the lasered myocardium.

DR. LEFEBVRE: As was stated earlier this afternoon, SPECT profusion is not the gold standard to correlate with angina and we cannot expect to have a hundred percent correlation. However, if you look at the changes that are clinically significant with respect to angina, at that point there was a concordance between the angina outcome and the SPECT outcome.

DR. SWAIN: Better than random. Okay?

Dr. Dawson, do you have a comment?

MR. DAWSON: Yes, I do. First of all, Mr. Dawson.

DR. SWAIN: Oh, excuse me.

MR. DAWSON: Dr. Dawson sounds better.

I am relatively new to the study. I have only been on it since last September. It has a long history.

With regard to Dr. Weintraub's question about the amount of attrition in the data, I think it is serious and I have come to the conclusion that even though there are some indicators that the sponsor has provided, such as the

comparison of SPECT and non-SPECT patients, even though there are some indications of comparability, so that that remaining subset of patients may represent the whole, if we could have the whole.

Also, as regards Dr. Edmunds questions about the concordance between profusion and angina improvement, I think it is weak. It is better in Phase 2 than it is in Phase 3, but I think the main thing comes down to the improvement in angina. And I appreciate the fact that they did take a 2 class definition for success, rather 1 class.

But what I remain concerned about are the possibilities that Dr. Casscells raised this morning about the possibility that the surgical patients had a better experience afterward based on the surgery itself and the psychogenic effects may be considerable.

I don't know what considerable is, but possibly it is. I would like to think that what Dr. Boyce indicated this morning about the comparability of the post-study course for the medical management and TMR patients are comparable. I would like to think that is the case. But where I come out on this is that the data are sufficient to

show prima facie that there is an improvement in angina, but I personal think that we need additional follow-up beyond the 12 months that has been accomplished and a greater number of patients as well.

DR. SWAIN: Dr. Weintraub.

DR. WEINTRAUB: A couple of things have already been covered. One of the questions I had asked and I know no one really has the answer is is six months long enough for a follow-up because really the 12 month data is very small and in a follow-up, what is an appropriate length of time for follow-up. Those are sort of rhetorical questions. I don't have an answer.

One of the things I wondered about -- if you look on page 121 and 122, a comment was made about the inclusion of subsequent -- about patients who had TMR and then had subsequent interventions, which had -- which theoretically would have been contraindications to TMR.

Let me go on with that. As I look at it, it would appear that some of those -- and I have checked off, I guess, 4121, 5104, 5122, 6120, et cetera. Some of these underwent angioplasties or CABGs to vessels which I suppose

may have been previously patent or uninvolved and now were involved.

Can you give me a breakdown on that a little bit?

MS. LEVIN: Absolutely. We actually have a back-up slide, which we can show you that shows exactly which patient fell in that category. While Terry puts the data, I can tell you that what we did is we looked at those additional procedures as whether they will have challenged the original study inclusion criteria or whether they would not. We considered a study as not changing the original study criterias if their vascularization was due to a de novo lesion or closed by graft. A preexisting lesion if it was on the right side of the heart, if it was a heart transplant or if it was a repeat TMR.

The slide is right behind you and we considered those additional intervention as potentially challenging the original inclusion criteria if -- where preexisting lesions on the left side of the heart. As you can see, grouping together the results for Phase 2 and Phase 3, there were an additional of 22 additional interventions done.

Of those, 14 did not challenge the original

inclusion criteria. There were three, which could have potentially challenged the original inclusion criteria and there were five for which we did not know why the procedure was done.

So, I think it is clear that those patients were clearly enrolled in the study.

DR. WEINTRAUB: One of the reasons I raised the question is because clearly if the PMA is granted, we then get into sort of off -- we haven't gotten into labeling yet, but I can foresee situations where coronary bypass will be appropriate in two areas of the heart and a third area is not bypassable. Will the surgeon then go and say, well, we will lase the part that is unbypassable.

As it reads now and as the application reads now, that would fall out of labeling. I am just -- do you anticipate that?

DR. LEFEBVRE: This is actually a very good question and which we hope we get to discuss as part of the labeling discussion.

DR. WEINTRAUB: Okay.

I only have one question and I am afraid I have

forgotten the gentleman's name -- Dr. Crew, you described the -- for lack of a better word, I guess, I would call it, the cast studies that you did with lased hearts. Someone asked whether you had such studies in controls. You may have misinterpreted that, not so much controls in this study or in this application but just controlled hearts; that is, hearts that had not been lased.

Could you answer that for me? What do they look like?

DR. CREW: The only controlled hearts that we had that we lased were rabbit hearts, but -- and tried to follow that, which were unlased hearts in control and we didn't see anything in terms of that, but these were just two cases.

DR. WEINTRAUB: No, I understand. But did you have other human cases not falling in this study, but have you done that procedure with other human hearts?

DR. CREW: No, no.

DR. WEINTRAUB: So, there are literally no controls then, human controls.

DR. CREW: No.

DR. WEINTRAUB: Thank you.

DR. CREW: I hope to get some but we don't have any yet.

DR. WEINTRAUB: That is all the questions I have.

DR. SWAIN: Thank you. The next, I think, voting member would be Dr. Parisi.

DR. PARISI: Thank you.

I wanted to come back to the issue of the variability in reading of the nuclear scans because I do think, at least the way I look at this, perhaps, it supports what Dr. Edmunds said, suggested. I heard that the variability was between minus and plus two segments. Is that correct?

DR. MANNTING: On the model with 25 segments and the total heart plus/minus 1.8 to be exact.

DR. PARISI: Well, if you look at that and round it off to the plus and minus two and turn back to this figure that was cited -- I guess it is -- I have it on page -- Section 1, page 14, or I guess the same figure is reproduced later on on I think it was page -- another page in Section 4, but this figure 5, I would look at that as between minus 2 and plus 2 segments as 22 patients really

fall within the reproducibility or the error of the method.

So, the majority of patients, as best I can determine, really don't have a change in profusion within the error of the method. Could you tell me that I am wrong about that?

DR. LEFEBVRE: Which figure exactly?

DR. PARISI: Section 1-14 is a summary figure, but it is reproduced also elsewhere in Section 4.

DR. SWAIN: I think 431, figure 5.

DR. PARISI: 431. I think it is the same figure. It adds up the same anyway.

DR. MANNTING: You would have to plot the plus/minus 2 on both sides and what falls inside that box is in principle within the limits of the reproducibility --

DR. PARISI: So, 22 of the 32 patients then are within the error of the method at the six month study?

DR. MANNTING: It seems to be in that order.

DR. PARISI: Thank you.

I also saw that 20 some odd patients had additional procedures, which probably involved cardiac catheterization and perhaps a ventriculargram was done.

Were any ventriculargrams done in subsequent evaluations of these patients?

DR. LEFEBVRE: I am not aware of ventriculargram being performed. Any of the investigators have done such studies? No.

DR. PARISI: Do you think that that might shed light on channels? I mean, I can see a millimeter on our ventriculargrams in my laboratory.

DR. LEFEBVRE: The only information I can share with you is I believe in Europe some people have used ventriculargram and the image showed some sort of a flushing into the myocardium. That is the only picture I know of.

DR. PARISI: You mentioned the data that was submitted in the PMA about echo cardiography and transesophageal echo cardiography seeing these channels. That, I take it, was with Dopler. You alluded to that and not with direct --

DR. LEFEBVRE: Actually, it was not done by TEE. It was done by transthoracic TTE. They used the same system mentioned by Dr. Horvath, a 512 system. They did a study on 14 patients at follow-up ranging from three months to twelve

months. Of those 14 patients, in 11 patients, they had images of -- within of quality so that they could look at the echo results of those 11 patients, 9 where they could see channels in 9 hole channels or transmural blood flow in 9 of those patients. All 9 of those patients were responders from an angina standpoint and also I believe the majority of those patients had shown an improvement in profusion studies.

The two remaining patients did not -- they could not see channels of transmural blood flow in those two remaining patients and those two patients were not angina responders.

With respect to how the measurements were done, yes, it was done by Dopler.

DR. PARISI: How do you reconcile that with the postmortem data that we have?

DR. LEFEBVRE: I think the autopsies may represent -- the patient died. So, maybe they died because there was no channels to begin with and maybe those patients were not responders. Now, I believe -- I am not an expert in pathology, but it seems like you have a lot of viability --

we are talking about viability in SPECT, but I think viability in histology studies seems to be even greater. I would say that we cannot use autopsy data to assess what the mechanism of GMR is.

DR. EDMUNDS: Were the echos TTE or TEE? Transesophageal or transthoracic?

DR. LEFEBVRE: TT, thoracic.

DR. EDMUNDS: Transthoracic.

DR. LEFEBVRE: That is correct. And that is why --

DR. EDMUNDS: How do you get the lung out of the way?

DR. LEFEBVRE: That is one of the reason why they could only observe the area close to the apex because they could not go deeper.

DR. PARISI: The procedure involves about making 30 punctures with the laser roughly on the average. Is that correct?

DR. LEFEBVRE: Correct.

DR. PARISI: On the heart we saw, there were two channels that were opened. It was digested away. What

happened to the other 28?

DR. LEFEBVRE: I think Dr. Crew can answer that question.

DR. CREW: On the heart you saw, there were probably 9 to 10, as far as we could tell, channels repeating sinusoidal areas. They came in a burst. What you saw the single of was is a vein draining away from that area. So, we felt that there multiple channels present, but we weren't sure how many because of the digestive process took six weeks and was real hard.

DR. PARISI: No further questions.

DR. SWAIN: Dr. Wittes.

DR. WITTES: We have been spending a lot of time on the missing data. I would actually like to go back to the randomization.

One of the problems -- and these are, I know, extremely difficult studies to do when you are talking about unblinded study with a dramatic therapy on one hand and what seems like a ho-hum therapy on the other. The question is this: How precisely did the randomization work? Where was -- how -- what was the process by which a patient came in

and was randomized in the -- and is there a lot of potential patients? And can you describe that both the way the protocol specified it and then how this was affected?

DR. LEFEBVRE: There was no log with respect to patient enrolled. However, speaking with a different site, we believe that the acceptance rate for participation in the study was around 90 percent. The way the randomization was conducted, once the patient had been identified and had met the study selection criteria, the site then called PLC Medical Systems. We then filled out a case -- an eligibility checklist, both on PLC site and on the clinical site as well.

If all of the questions required on the eligibility checklist were met, that is, if the patient met the study selection criteria, at that point the randomization assignment was given by PLC to the clinical site. That randomization assignment was followed up by a fax transmission.

DR. WITTES: What was the block size? How did you get block sizes at the various sites?

DR. LEFEBVRE: Six.

DR. WITTES: What percentage of people who were -- that you randomized entered the study?

DR. LEFEBVRE: We believe -- we had a few patient drop out after the study and we can give you the exact number, but out of the 200 patients, it is less than 5.

DR. WITTES: Okay. Okay. Great.

The next question is a completely different question. It has to do with -- there looks to me -- I mean, the data are suggesting, showing, a very strong effect on unstable angina. I would have thought that that would have translated into some sort of an effect on mortality and, yet, there is none.

Do you -- have you done any calculations that would show what kind of effect on mortality you would have predicted for the observed effect on unstable angina? And can you explain the apparent discordance?

DR. LEFEBVRE: Actually, for those group of patients who were enrolled under early condition of unstable angina, the mortality rate, both perioperatively and follow-up mortality was higher than --

DR. WITTES: I am not talking about that group. I

am talking about the group in -- I am talking about the randomized group.

DR. LAVIN: Phil Lavin. From a statistical point of view, looking at the one year outcomes and looking at that, you probably have with a hundred per group about, I would say, 85 percent power to pick up about a 10, 12 percent difference between groups that far out. It is almost a doubling of the hazard rate. So, I would say, you know, more follow-up would be needed in order to nail down any kind of survival differences.

The thing that I was struck by was that early survival dip for the TMR group that eventually was catching up and it is like some of these classical, you know, data for -- that you look at for CABG. Who knows how far out one will have to go in order to see that survival advantage translate?

So, yes, I think that with further follow-up, one might be able to see a difference, but clearly a larger n would be needed for that endpoint.

DR. LINHARES: On the subject of death, on the mortality data, Dr. Cohn would like to make a comment.

DR. COHN: This is related to long term mortality.

First of all, the sponsors, I think, did a very -- I guess, requirement and a very fair job. They included every single mortality. One of the patients in that series, which, by the way, in our series is a hundred percent followed up for four years -- one of the patients died at six months, having been burned to death in a house fire. I don't think the laser had anything really to do with that.

But they scrupulously kept all of the people involved in the mortality curve. Also, they included the perioperative mortality and the perioperative mortalities, 4 percent in the Phase 3 and, I think, 9 percent in the Phase 2, are, obviously, significant, but if you consider the end stage nature of these particular patients -- and I would venture to say most of these surgical clinicians here would agree that a double or triple re-op CABG with a rejection fraction of 20 to 30 percent with lousy end stage arteries, which is the kind of patient we are doing in this study, by the way, would have a mortality of 10 to 15 percent without any equivocation at all.

So, this is a very, very difficult group. I think

the perioperative event -- they did not do a separation of the perioperative mortality from the total mortality, which I think is -- you have got to do what they did, but also I think that would have been of interest had they done this to compare that as well and might be more illuminating.

DR. SWAIN: But everyone that has a 30 percent EF, there had to have been a 70 percent to make this average 50. In a house fire, if you have an infarct or an arrhythmia and drop your cigarette, you burn up or have a car accident --

DR. COHN: Well, surely, Madame Chairman, you are not saying that they had an infarct, dropped a cigarette and caused the house to burn on fire, are you?

DR. CALIFF: I would like to comment on that. Those of us that have served on event committees see that kind of thing all the time. It is almost impossible to separate out cause of death. So, I don't think it is unplausible.

DR. COHN: No, they did that, but I think it has to be considered in your thinking about the causes of death involved.

DR. WITTES: But I guess the import of the question for me has to do with the question that has arisen several times, whether the unstable angina that you are seeing in the treated group is the same unstable angina as you are seeing in the non-treated group. Because if it were, then you would, I think, expect a differential mortality and if it weren't, then that would be consistent with seeing no differential mortality.

That is really the question that I am asking.

DR. LEFEBVRE: The definition for unstable angina was, obviously, the same for both treatment groups. However, what you have to take -- you have to keep in mind is that the unstable angina event, the admission to an ICU for two days was the event that triggered the possibility for the patient to cross over and receive TMR.

So, we did not follow the patients beyond that unstable angina event. If those patients had been followed in the study for beyond that event, maybe the results that you are mentioning would have occurred. We did not get the opportunity to see that because those patients crossed over after this event.

DR. WITTES: Would it be possible to follow -- supposing at this point you were to say let us go -- we have these 200 patients, minus the ones that are no longer alive, can you get -- could you get follow-up information on all of those, even the ones you dropped? Could you pull them in and get images from them? Would that be possible?

DR. LEFEBVRE: I am confused. We don't drop any of the patient. I mean, we are going to continue following -- all the patient that we can follow, we follow them. We will follow them per the time of the protocol. Not all of them have reached 12 months, but they will be followed and those patients who crossed over are followed as well for 12 months.

DR. WITTES: I got confused on what you just said.

Okay. Let me ask just one other thing. I think everything else has been covered.

There has been a lot of discussion about the concordance between the angina and the SPECT results and these are very hard. I mean, I know statistically this is very hard to do because there are all kinds of ways of measuring it, measuring concordance and discordance when you

have noisy data on both sides.

Were there prespecified ways of measuring concordance?

DR. LINHARES: No. This is all post hoc analysis.

DR. SWAIN: Dr. Vetrovec, can you just give me an idea of -- do you have a moderate number of questions?

DR. VETROVEC: Not a long list.

DR. SWAIN: Okay. Why don't we have Dr. Vetrovec's questions and then we will take a break.

DR. VETROVEC: I just want to make a couple of comments from a very clinical standpoint. One of the things that clinicians see bypasses doing is particular improving the outcome for high risk patients and you have got a big spread in LV function. Dr. Cohn points out that these were terribly high risk patients and, yet, the average ejection fraction is 50 percent. I am a little unclear as to where they really fall in terms of one of the high risk categories. It really hasn't been discussed here.

I would be interested to know whether your mortality, particularly perioperatively or even long term, is in any way correlated to LV function rather than all the

other parameters we have been looking at.

DR. LEFEBVRE: There was actually a statistically significant relationship between a lower baseline ejection fraction and the incidence of perioperative mortality. The lower the ejection fraction, the higher the mortality rate.

DR. VETROVEC: How about long term?

DR. LEFEBVRE: That existed as well. The data is shown for Phase 2 in page 42 of the panel package.

DR. VETROVEC: The other question I would ask relates to diastolic function. We have talked a lot about systolic function. But one of the points was raised as to whether or not in some of the autopsy findings, there might have been some evidence of fibrosis where these holes were created. I think that is an area where we don't often look at, but is there any information from either echo cardiographic or the radionuclide filling studies on left ventricular performance that would suggest a change in diastolic function.

DR. LEFEBVRE: Dr. March can answer that question.

DR. MARCH: I am Robert March.

I alluded to this a little earlier. This is not

in the PMA, but the 17 patients at one year looked at with mugus(?) scan as far as acceleration of filling and a diastolic compliance. No change with this carbon oxide laser. No change in systolic performance at one year in those 17 patients with complete follow-up, baseline, three, six and twelve month scans.

DR. VETROVEC: That is diastolic as well as systolic. Four parameters were looked at.

The other question I have is there seems to be a lack of any type of documented consistency between centers in this study in terms of what was done. Was there at least a core lab that reviewed the angiograms to be certain that the inclusion criteria were similar between -- and really fit the protocol.

DR. LEFEBVRE: There was no core lab to review the angiogram prior to surgery.

DR. VETROVEC: And I guess just lastly a comment --

DR. LEFEBVRE: If I may just continue.

As we have shown and talked about earlier, there was no difference in the outcome between the different

sites. And that was true for both the controlled patient or the TMR patients.

DR. VETROVEC: The last thing, I would still like to get at is the postulate of why patients have such a striking decrease in angina and such a limited decrease in profusion abnormalities. One thing that worries me a little bit is the echo -- I mean, the nuclear analysis individual indicated that there was a lot of variability, that these weren't perfect tests. I am just still worried about the whole issue of silent ischemia.

If you look at the ASEP(?) trial, that, at least suggests those are the patients that are risk.

DR. SWAIN: Okay. We will have --

DR. LEFEBVRE: Can we respond?

DR. COHN: I think you are alluding to the placebo effect.

DR. SWAIN: Dr. Larry Cohn speaking.

DR. COHN: Dr. Larry Cohn from Boston.

And that certainly is, obviously, the most vexing sort of thing. As you see, we are still working on the mechanism and I think it is personally primarily

androgenesis from our lab, but species -- the only thing I can say is that -- and I think there is some statistical caveats that show this is not a placebo effect, but I will let the statistician talk, but in our particular series, we have not done a whole lot of patients. We have done maybe -- of the first part, we did about 10 percent of the Phase 2 and about 5 percent of Phase 3 because we are picking the patients, as I said, on those very strict criteria, as most are.

We followed these patients now for four years because we started in 1992. That is, I think, the relevance of the Phase 2 trial. I am not a master clinical scientist, but I am very, very -- would be very surprised if a placebo effect lasted for three years. We take a totally Class 4, clearly disabled patient and they are doing reasonably well with decreased medications for a longer period of time.

Now, the panel has expert testimony to the contrary but, to me, this is the most -- and we have a 100 percent follow-up in our series. We followed every single patient for six months as long as we have been doing the study. So, to me, the sustained clinical effect in 75

percent of the patients over two years is a suggestion to me this is definitely not a placebo effect.

Perhaps the statistician would like to comment on that as well.

DR. LAVIN: You know, I think it is -- this is very much in follow-up to the comment that was made this morning by the first FDA speaker, relating to the placebo rates and one of the articles referenced in there was the Benson article and I went back, we looked at the Benson article and we saw for some of the different types of procedures performed, there were in the fifties and the sixties some mammary artery ligation studies done and in there the response rates or the placebo rates, as they called them in those surgery studies, was around 35 percent.

I looked back at some of the original papers that were referenced there and most of them were -- they were transient, short, you know, usually not lasting more than six months, but 35 percent was about as good as it got. In contrast to drug as placebo, that was around 35 percent also. So, intuitively, one looks at that population with its 35 percent and saying can we get 70 percent, 75 percent

success rate here, with a more rigorous definition of angina success than what is in those original old trials and with that, my thinking is that dog doesn't hunt.

There is no way in the world you are going to get a 75 percent response rate or success rate here and in contrast to a placebo, you know, rate being that high. So, intuitively, it just doesn't -- the hat doesn't fit. So, I think the 75 percent that we are seeing here in a randomized setting is something that is credible and believable in the big picture.

DR. SWAIN: Dr. Casscells.

DR. CASSCELLS: The placebo effect implies that the patient feels better and is ignoring their symptoms or something. It is a little bit more than that. In fact, it is a lot more than that. If patients cut out their cigarette smoking and they change their diet and they start exercising and they have hope and all these things, this has a huge payoff.

You know, some years ago when I was at the National Heart, Lung and Blood Institute, we looked at some of Dr. Vineberg's living patients. We were only able to

persuade six to come in for cardiac catheterization. One might suppose that some of the patients who are doing very well were not included in that group.

Those patients had coronary artery disease. He hadn't operated on anybody unnecessarily. Of the six grafts we looked at, of the six internal mammaries tunneled through the myocardium, with six or seven side branches cut to profuse the anterior wall. One of those was getting real good blood flow and I would venture to say that it was supporting that patient's life.

Now, keep in mind these were patients who had been operated on by Vineberg a couple of decades later. So, there is sort of a selection in favor of survival, but we were only able to show benefit in one of six. Nevertheless, that was very important to that one patient.

But the key thing that came out from talking to Dr. Vineberg and to Dr. Vineberg's patients was that he threw them out of the hospital if they wouldn't quit smoking. Dr. Vineberg was a good surgeon but he was a great internist and it is very important to realize that surgery gets your attention. If somebody like a Bud Frazier or a

Larry Cohn is telling you -- wagging their finger in your face, don't smoke those cigarettes or I am not going to be your doctor anymore or don't smoke those cigarettes, you are going to die, that has a huge impact.

So, we are not talking about placebo. We are talking about what exactly is the mechanism. I have very little doubt that these patients are doing better after this surgery, but it is very important to know why they are doing better.

DR. LEFEBVRE: You had mentioned as one of the parameters the potential use of rehabilitation centers. None of the patient, neither in the control group nor in the TMR group underwent rehabilitation.

As far as smoking, the information that we have indicated that there was no significant decrease but --

DR. CASSCELLS: Well, let's see that data. Now, look, right here in your own data, Doctor, you have got data on the septum and the inferior wall that can either make or break your case today. Now let's have you look at that. The key is this: If the patients who underwent TMR have an improvement in the septum or the inferior wall and the

patients who did not undergo TMR have a deterioration in the septum and the inferior wall -- these are the non-laser-treated segments -- that suggests something is going on that might have to do with medications or diet or cigarettes and so forth.

Now, on page 31, there is a little data and I think we need the statisticians to help on that, but you do have data on the anterior wall and on the whole LV, but you have merged that data. You need to separate out the septum and the inferior wall and let's find out what happens to those patients. That may support your case.

DR. LEFEBVRE: We actually treated the inferior wall. The inferior wall was treated. The only region which was not treated was the septum.

DR. CASSCELLS: Okay. I am sorry. Well, let's look at the septum and see what happens. It looks to me like on page 31 -- 430 -- on page 430 --

DR. LEFEBVRE: To answer your question, if you look in the TMR-treated patient, there was an improvement in septal profusion. If you look in the controlled patient, there was no such improvement. But since we do not

understand exactly what is the mechanism behind TMR, whether it is a direct or an indirect profusion mechanism, I do not know how this change in septal profusion could make or break the case.

DR. CASSCELLS: Well, let me suggest to you that indicates to me that surgery has gotten the attention of these patients and you have done them some good and they have changed their life, I suspect, and this has a tremendous effect. In the recent Lancet trial of just diet, Mediterranean Heart Diet, 45 percent reduction in mortality in one year just with a change to a Mediterranean diet.

These kinds of interventions are very, very important and it is important to deciding -- it is a separate issue. Is it worth opening someone's chest and drilling some holes in to get their attention? And it may be. It may be in the worst case.

DR. LEFEBVRE: I think Dr. Frazier would like to answer that statement.

DR. FRAZIER: Well, there were only 10 percent that were smoking to start with. I must say I approached this trial was as a totally randomized. What you said is

generally true. Most of these patients, particularly in this Phase 3 study, they went home in a couple of days, a couple or three days at our center. I really didn't talk to them before they left and I certainly didn't try to influence them one way or the other, just for the reasons you alluded to.

The only way to really do this study -- and this should have been spelled out by the FDA before this company ever embarked on this -- are you -- do you have to show the mechanism of action to be approved. That should have been very clear at the start. It wasn't. They approved an angina study and a thallium study, which this company has diligently done.

As far as the medications, we didn't alter any medications they were on. Certainly, the placebo effect to be carried out to its real point would be to do an operation, a sham operation, on the patients you did nothing to. Now, is that the advice -- is that the advice of the panel? Is that the advice of the FDA? How would we do that ethically?

DR. SWAIN: Let me say that safety and efficacy

are what we are asking about and I think what I hear the panel members so far asking for is complete data or not complete data, but data that is comparable to other good trials.

And we are going to have a break, guys. We have got to do this. It is sort of a requirement.

Let me ask one thing. Tom Callahan, do you have a comment about the FDA's design of studies? Did you design the study?

DR. CALLAHAN: No, we typically don't design studies. We try to influence studies but companies design the study and then we approve it or not, but the studies -- and as we get closer and closer to the real time now we are trying to influence studies a lot more, but usually what happens is the companies design the study and then we approve it in terms of patient safety.

DR. LEFEBVRE: The study was designed with your collaboration. It was designed two years ago.

DR. FRAZIER: The randomization was stopped in September with agreement by the FDA.

DR. CALLAHAN: The study was stopped because there

were a fixed number of patients that were designed to be in the study and when you reached that study number, the study was stopped.

DR. FRAZIER: It was satisfactory. It was clear. You agree?

DR. CALLAHAN: No, I agree that we stopped the study because you reached the defined number of patients. That is as far as we went, that you reached the agreed upon number of patients that you were going to do.

DR. CALIFF: I think we need to clarify who is asking the questions here. This is outside of --

DR. SWAIN: We are concerned about quality and quantity of data, what I have heard. I think if there were --

DR. LEFEBVRE: If I may state --

DR. SWAIN: No. Hang on, guys. That is the main concern. We sort of have to get this ended right now. The FDA does not design the study. They approve a design that is made -- the company has the responsibility for essentially convincing the advisory committee that there is science and that there is good quality and quantity of data.

So far, virtually everything I have heard is comments about quality and quantity.

We are going to come back at 3:30 and see if we can figure this out.

DR. LEFEBVRE: If I may just add, the study was stopped not only because the number of patients enrolled -- to be enrolled was reached, but also because the result when comparing TMR to controlled patient from morbidity and mortality standpoint were very different.

DR. SWAIN: Yes. Well, we just have to see if we agree with that.

[Brief recess.]

DR. SWAIN: Okay. The plan for, I think, the remainder of the afternoon is that we have two more panel members to ask questions, Dr. Tracy and I. And then I am going to ask the panel members if there are any absolutely pivotal questions they need to ask the company.

Then we are going to start the panel discussion and what the options are for what needs to be done the rest of the afternoon.

So, Dr. Tracy.

DR. TRACY: Thank you. I know this is getting to be a long day. So, I will try to be as brief as possible.

One thing that I think has struck a number of people is what you might call a discordance between the, if you would, objective data either by PET or thallium versus the rather dramatic improvement in the anginal symptoms. I would just like to ask, if you go back, the first symptom assessment was taken when, post TMR?

DR. LEFEBVRE: Three months.

DR. TRACY: Three months. And on page 431, just looking at the people, there were 29 people who experienced symptom improvement, if I am right, at three months, on 431? If you count both the symptoms better scanned worse and symptoms better scanned better, so there is a total of 29 patients. So, around 31 percent had an improvement in their anginal symptoms in spite of a worsened thallium study.

I need an explanation for that. I need an explanation first for those 31 percent that improved. There must be another mechanism that is taking place.

Secondly -- and I am not asking you to tell me what the mechanism is because I don't think you can come up

with a mechanism. Is that --

DR. LEFEBVRE: I can't tell you what the mechanism is. I think that has been made clear by the panel today.

DR. TRACY: If angiogenesis or if some kind of improvement in blood flow is expected to be responsible, is three months a reasonable amount of time to expect to see an improvement in blood flow?

DR. LEFEBVRE: Again, we run into a mechanism but what the company believes, it is not going to be one mechanism that is going to be responsible for the improvements in follow-up. It may be a combination of mechanisms. Maybe initially since the patients are discharged from the hospital within a few days without having symptom, there may be at that point a direct profusion, which then can correlate, can transform into an angiogenesis, a growth effect, which then is going to take a few months. So, that is what you are into, the progression.

DR. TRACY: And your PET data, as I understand it, is also looking at profusion. There is no data that you have given that has really come to the issue of viability. Is that correct?

DR. LEFEBVRE: I believe the PET data published was on profusion. It wasn't on viability.

DR. FRAZIER: That is wrong. The PET data -- the reason we did the PET to start with was that we had to demonstrate in these patients that a decreased profusion to viable myocardia, that the myocardium was viable at the start of the study. So, we knew the myocardium was already viable. So, you don't do another study to show that it is still viable. It was very expensive to just do the profusion studies.

DR. TRACY: Okay. At least some of the animal data that you have presented would indicate that -- there is a paper in there referred to by Dr. Landrow(?) that reports an animal study, which showed no improvement in blood flow tissue pH high energy phosphates and you also have another paper that is the packet that -- by Dr. Whitaker that suggests that there is increased fibrosis surrounding the channels, the laser channels.

Any comments on that?

DR. HORVATH: The papers that you are referring to are not -- are really not part of this study as far as the

clinical trial is concerned. We are addressing mechanism -- we do not have, obviously, as you have heard countless times today, an exact idea of how it works.

The fibrosis that you are seeing is typical of what you would see after an injury with the laser and that is what those papers documented. Now, the measurement of profusion, there are studies that show that there is improved profusion both radionuclide and colored microspheres in the laboratory.

But, again, these are research experiments that are trying to uncover the mechanism, but really aren't related to the patients per se. I think the other thing in those studies that you are referring to, they were not done in a model of chronic ischemia, so it is completely unlike the clinical scenario that we are addressing.

DR. TRACY: Okay. Before you leave, actually I had -- you had made a comment earlier regarding the denervation that is seen with catheter ablation and trying to draw a corollary to that. We have published on that and there is a rather dramatic change, at least in the perimeters you can measure heart rate variability related to

two versus ten heart hits. It doesn't really matter.

If we can cause that dramatic of an effect with a fairly focal -- a single focal burn, I would expect drilling 31 holes into the heart would probably significantly alter the autonomics of the myocardium. So, before you discount that as you are thinking of future things to look at, I would strongly consider that in doing studies, such as MIBG or heart rate variability or other things to try to get at that as a potential mechanism of benefit for these people.

DR. HORVATH: The studies that you are referring to with radio frequency ablation, you saw improved profusion?

DR. TRACY: No, we didn't look at profusion.

DR. HORVATH: And increase in angina?

DR. TRACY: No, we weren't looking at -- I am not referring to -- I am talking about alterations in autonomics. I think there may be some alteration in autonomics.

DR. HORVATH: So, when those patients were stressed later, they had a decrease in their blood pressure?

DR. SWAIN: We actually have questions mostly that

way.

DR. TRACY: I am not saying there is anything that an ablation will do to improve myocardial profusion. I am just stating that a direct myocardial hit either by laser or by radio frequency energy is going to alter the autonomics of it. It is going to denervate or do something different to the autonomics of the heart.

Don't discount this as a potential mechanism of improvement in your patients. I think that is a mechanism you haven't adequately explored in this data.

DR. HORVATH: I agree with that and I think that we are not discounting it. I think that on the other hand we are not saying that we are totally deenervating the heart and setting up a harmful situation.

DR. TRACY: As pertains to that, your incidence of arrhythmic events does seem to be quite high and on your one slide in your initial presentation this morning, you talked about 38 percent incidence of arrhythmic events in redo CABG patients. That, I believe, was from a meta-analysis but it is kind of lumping together life-threatening and non-life-threatening. I am not sure that that is a fair comparison

to make to this rather startling incidence of arrhythmia seen in these patients.

DR. LEFEBVRE: We can give you the references that were used for that analysis.

DR. TRACY: I would ask you if you think that that really is a fair comparison.

DR. LEFEBVRE: We think it is a fair comparison when you look at the overall incidence of arrhythmia, when you look at the TMR patient and adding them together, then, if I am not mistaken, the percentage of incidence is in the 25 percent as opposed to in the thirties for the redo bypass surgery.

DR. TRACY: I just need an explanation on page 108 for the perioperative mortality that you report a 6 percent in the control group. What operations are these people having in the control group that gives them the 6 percent mortality?

DR. LEFEBVRE: Actually, they did not have an operation. They just died within one month of being enrolled in the study.

DR. TRACY: Okay. So, that is just for lack of a

better place to put that number.

DR. LEFEBVRE: That is correct.

DR. TRACY: And I guess it is abundantly clear that there is not a mortality benefit to this procedure either.

DR. LEFEBVRE: The data shows that the mortality is similar for the TMR group and the control group. What is different is the benefits.

DR. TRACY: Okay. Do you have any information on patients who have had fatal myocardial infarctions in the TMR-treated group -- treated areas after -- if a person had a myocardial infarction after having laser treatment in the area where laser treatment was given, was there an increase in mortality compared to the control group? Was a fatal MI more likely after TMR as opposed to a non-fatal MI?

DR. LEFEBVRE: I don't think we have the information capable to answer that question.

DR. SWAIN: It is Dr. March speaking.

DR. MARCH: Just very brief. One thing we did learn about all of these 400 patients or whatever it is is that the timing of doing this procedure is very important.

So, if you do it in the face of evolving myocardial infarction or you were fooled and didn't realize you were in that situation, it is a very, you know, deadly situation. So, the chronic stable angina patient, where you are sure that they are in a period of clinical stability is the most ideal clinical situation that the investigators have learned to apply this therapy.

So, I don't know that it would necessarily make it worse, but if it takes six weeks for them to get clinically better, which is what we see, they don't have time to recover that far and deal with the stress of the operation on top of the stress of the myocardial infarction.

DR. TRACY: I guess I am still worried about all the sudden deaths and I just -- I don't know if you can do some type of predictive sudden death in the patient population versus observed sudden death. It just seems quite high.

DR. LEFEBVRE: We just looked at the mortality rate at follow-up, excluding the perioperative mortality and there was no difference between the control group and the rate of death in the control group versus the rate of death

in the TMR group.

DR. TRACY: I think in light of the length of the day, I will cut it at that.

DR. SWAIN: I hope I have only three quick areas of discussion.

First of all, we are talking about the control group and medical treatment, which we, as surgeons, have to believe that medical treatment actually works in these patients, Dr. Casscells was discussing. Can you tell me just simply, do you have any measure of medical -- taking medication compliance, not what was prescribed -- we have got that data -- but were there any compliance measurements of whether these patients took their medicines?

DR. LEFEBVRE: You mean whether the patient took -- no, we don't.

DR. SWAIN: Okay. Thank you.

How many of the patients in the TMR group versus a control were smoking at 12 months?

DR. LEFEBVRE: The case report form doesn't track that information directly. The previous statements were made by the investigator on their own experience.

DR. SWAIN: Okay.

Cardiac rehab, did someone mention that absolutely no patients that had surgery of these chronically Class 3 and 4 anginas had cardiac rehab? I would find that incredible. I want the aggregate group -- aggregately, how many patients with TMR had cardiac rehab?

DR. LEFEBVRE: Again, that is not information that we have. We cannot give you the actual numbers. It was based on the -- from the investigators.

DR. SWAIN: I assume it is not correct that they didn't have rehab. Dr. Frazier, did any of yours have rehab, cardiac rehab, post-op patients?

DR. FRAZIER: The average duration of therapy in our patients was nine and a half years for angina. These patients were not patients who were unfamiliar with the care of chronic angina. They had chronic angina and they went back to their usual standard of care. This wasn't a bypass. It was a procedure that we were investigating under rather rigorous criteria.

DR. SWAIN: How many of your control patients then were in a cardiac rehab program, former cardiac patients?

DR. FRAZIER: It was the same. I mean, if they were in it before, which, again, these were patients with an average of nine and a half years of therapy.

DR. SWAIN: Okay. So, we don't know that. That is, I guess, one of the bigger problems I have is that comparability of groups, especially when we are dealing with a soft endpoint.

Then the other point is that has been brought up is inter-site variability and Dr. Lansing has got the biggest group and I have actually spent a few years trying to find people with normal ejection fractions who have absolutely unbypassable or uncardiology interventional arteries.

Dr. Lansing, I just wonder, you have had 54 patients in two years. What is the denominator? How many patients did you do isolated coronary bypass on in those two years, just a guess on the number?

DR. LANSING: 400. Our group would have done about 2,200.

DR. SWAIN: But your --

DR. LANSING: If they are castoffs from the rest

of the group, I get them. This is the junkyard of cardiac surgery.

DR. SWAIN: Yes. Dr. Cohn, what -- oh, Larry is not there -- the next biggest group, I think, Bud or Dr. Frazier, you did a fairly big group. Like what do you think your percentage of patients that would fit this protocol versus classical coronary bypass.

DR. FRAZIER: None of these patients would have fit classical coronary bypass.

DR. SWAIN: No, no, I am saying how many regular coronary bypasses would you say you did? You did, what, 17 probably of these or so? During this enrollment period, going back two years.

DR. FRAZIER: About 3,000. Of course, these were referred specifically for this. They were judged not -- there is no inoperable or non-dilatable patients. Now, we know that and that is a misstatement, I think, in the company's premise. You can always bypass patients. You can always dilate them, but there are people that are optimally not optimal for the procedure. So, that, I think, would be better phraseology.

DR. SWAIN: Right. I was just looking at the variability because it would seem that there is probably less patients at some high volume institutions that qualified for the study and a lot more at others and variability of treatment seems to be fairly substantial.

The only other I have is -- Dr. Friedman is a consultant to the panel and -- panel discussant, excuse me -- my question is when we look on page 95 of the people that had SPECT and didn't have SPECT, what concerned me was that 13 percent of the ones that didn't have imaging were smokers versus 3 percent with a P less than .05 and I don't even know what that P value was; probably a lot smaller than that.

I disagree with the FDA reviewer that is saying that there appears to be no bias in selection. I think that -- if you use that as a marker for compliance -- I think also the patients that have the least good results tend to not continue in follow-up.

You are very experienced in clinical trials. Tell me how you view missing data? As equal?

DR. FRIEDMAN: No, the burden is the other way

around, obviously. Just because something is not statistically different does not mean that it is the same and does not mean that those who have had the measurement are the same as those who have not had it and, of course, this doesn't break it down by the treatment group either.

So, I think the concept of missing data here is an extraordinarily important one and I gather there was a lot of discussion on that that I am sorry I missed this morning. If you have any appreciable amount, it really does raise a serious question as to the interpretability of the results.

DR. SWAIN: Dr. Califf, do you have a comment as another big clinical trial person?

DR. CALIFF: I think if you go to clinical epidemiology 101, the first thing you are taught about primary endpoint is that if you are missing substantial amounts of it, you can jump through all kind of hurdles and turn somersaults but you can never be sure that you have corrected a postrandomization bias.

DR. SWAIN: The next phase is, I think, we will ask panel members, whoever has pivotal questions to ask to the company.

Dr. Califf, I know you do.

DR. CALIFF: I just want to make sure I understand one thing that was alluded to. It is on the mortality data, again, just to make sure I really understand how things are being counted because I got confused when the question was asked.

In the 101 patients in the intend to treat analysis, if a patient underwent a TMR procedure or crossed over within the first 30 days, say, and then died during the perioperative period, where does that event show up on the Kaplan-Myer curve? And you tell me the 12 intent to treat perioperative mortality deaths, none of those patients actually had surgery.

DR. LEFEBVRE: Could you tell me which page you are looking at?

DR. CALIFF: Page 108.

DR. LEFEBVRE: With respect to the intent to treat analysis, the patients were followed -- the follow-up duration, the timing during the study was counted from the time of enrollment; that is, that if the patient was enrolled in the study, then at five months follow-up,

crossed over, then died during the following month, that death is included in the intent to treat analysis, has a six month death because the intent to treat takes into consideration the start of the study as the enrollment.

DR. CALIFF: Right, but you said the 12 patients at the top there, who are listed as perioperative mortality, that none of those patients had TMR. Did I understand that correctly?

DR. LEFEBVRE: No, you misunderstood me. What I am saying is that in the column on the right, when you look at control, no crossover, those patients, those three patients who died in the perioperative period died and did not have any intervention.

DR. CALIFF: So, out of the patients who were randomized to control, there were a total of 18 deaths. That is the intent to treat group.

DR. LEFEBVRE: That is correct.

DR. CALIFF: I just wanted to make sure I had that right here. And 12 out of the 18 deaths occurred after they crossed over and had a TMR procedure. Is that right?

DR. LEFEBVRE: That is correct.

DR. CALIFF: And those deaths -- I just want to make sure, again, in the Kaplan-Myer estimator below, you didn't censor patients if they crossed over with regard to mortality in the intent to treat analysis.

DR. LEFEBVRE: No, no, no, no, no. I mean, with the intent to treat all the patients are counted in the analysis.

DR. CALIFF: It is another interpretive issue. If two-thirds of the deaths occurred after the procedure that you are evaluating in the control group and then you say the mortality rates are the same, it is hard to --

DR. LEFEBVRE: That is the intent to treat analysis.

DR. CALIFF: I understand. It just points out the difficulty, I think, when you have so many crossovers.

Then with regard to page 120 then, I presume that you did the same thing; that is, if a patient had crossed over and had TMR and then --

DR. LEFEBVRE: Actually, on page 120, you are looking at the global endpoint, the incidence of death, Class 4 angina or unstable angina. Since we didn't require

to crossover was the unstable angina event, those patients would be counted as having had the event and the crossover period would not be taken into consideration in the analysis.

DR. CALIFF: Okay. That is what I needed to know. Thanks.

DR. SWAIN: Dr. Wittes, did you have a --

DR. WITTES: Now I am confused. I thought what he had said was that the 12 people in the intent to treat, who were called perioperative mortality, were people who died within the first month after randomization. Now what you are saying is people who died within the first month after TMR.

DR. LEFEBVRE: No, no, no, no. In the intent to treat, those that occurred within the first month of enrollment, some of those patients crossed over within the first month and then died.

DR. WITTES: It is a mixture.

DR. LEFEBVRE: It is just that as we have been -- has been requested by the FDA, we presented the data in different ways. We presented it with a regular control

group in which the data are the patients recounted into crossover. We presented it where all the crossover patients was excluded and we also did it in intent to treat analysis.

DR. CALIFF: Now, I am confused again now.

DR. LEFEBVRE: I am getting confused, too.

DR. CALIFF: If you take all the deaths in the control group, what -- how many of the deaths occurred after crossing over versus those that occurred without crossing over.

DR. LEFEBVRE: If we go back to your page, which was, I believe, 108, there were six deaths which occurred in the medical management while on medical therapy. Okay?

DR. CALIFF: Right.

DR. LEFEBVRE: Then there were 18 deaths in the intent to treat analysis. That leaves you 12 patients who died after crossover.

DR. CALIFF: Okay. I understand.

DR. SWAIN: Better stop there while you both understand.

Any other panel members have questions for the company?

DR. EDMUNDS: I am going to ask you to refer to 50 percent of your autopsy data on page 156. It is patient ID 8003. It says, and I will read it, just above -- seven or eight lines above "Classification," "The epicardial surface of the left ventricle in the region of the TMR procedure show diffuse telangiectasia. There were no grossly patent laser channels. Linear transmural myocardial scars were seen extending from the epicardial to the endocardial surface corresponding to scarred laser channels."

This is 50 percent of your autopsy data and I think it shows that you have scarring caused by these lasers, not nourishing holes.

DR. LEFEBVRE: Again, that is the patient who died.

DR. EDMUNDS: Well, that is the only way you can get an autopsy.

DR. SWAIN: Any other questions?

Dr. Wittes.

DR. WITTES: I have one question about -- one more question about who was in the analysis.

The way I am pulling the numbers together -- and I

just want to make sure this is right -- there are 97 treated, 101 control. Of the patients who had both an angina and an imaging done at three months, there were 37 in the treated and 26 in the control and at six months, 32 and 21. Is that right? So, a third of the patients in the treated had both at six and the --

DR. LEFEBVRE: You seem to have the right data.

DR. WITTES: Okay.

DR. SWAIN: Okay. We will ask Dr. Stuhlmuller to read the panel options. What we are going to do is make sure all the panel members understand the options for motions here and what we should be doing. Then we will discuss among panel members the feelings about which of the options should be chosen and then eventually we will have a vote and then eventually we will discuss what we voted on and what our recommendations are for further extension after either of the three recommendations.

DR. STUHLMULLER: Okay. The panel recommendation options for premarket approval applications: The medical device amendments to the Federal Food, Drug and Cosmetic Act require that the Food and Drug Administration obtain a

recommendation from an outside expert advisory panel on designated medical device premarket approval applications that are filed with the agency.

The PMA must stand on its own merits and your recommendation must be supported by safety and effectiveness data in the application or by applicable, publicly-available information. "Safety" is defined in the Act as reasonable assurance, based on valid scientific evidence that the probable benefits to health under conditions of use outweigh any probable risk.

"Effectiveness" is defined as reasonable assurance that in a significant proportion of the population the use of the device for its intended uses and conditions of use when labeled will provide clinically significant results.

You recommendation options for the vote are as follows: Option: Approval. There are no conditions attached.

Option No. 2 is approvable with conditions. You may recommend that the PMA be found approvable subject to specified conditions, such as resolution and clearly identified deficiencies, which have been cited by you or by

FDA staff.

Prior to voting, all the conditions are discussed by the panel and listed by the panel chair. You may specify what type of follow-up to the applicant's responses to the conditions of your approval recommendation you want, i.e., panel or FDA.

Panel follow-up is usually done through homework assignments to the primary reviewers of the application or to other specified members of the panel. A formal discussion of the application at a future panel meeting is usually not held.

If you recommend postapproval requirements to be imposed as a condition of approval, then your recommendation should address the following points: the purpose of the requirement, the number of subjects to be evaluated and the reports that should be required to be submitted.

Option No. 3, not approvable. Of the five reasons that the Act specifies for denial of approval, the following three reasons are applicable to panel deliberations:

(a) The data does not provide reasonable assurance that the device is safe under the conditions that you have

prescribed, recommended or suggested in the proposed labeling.

(b) Reasonable assurance has not been given that the device is effective under the conditions of use prescribed, recommended or suggested in the labeling.

(c) Based on a fair evaluation of all material facts in your discussions, you believe the proposed labeling to be false or misleading.

If you recommend that the application is not approvable for any of these stated reasons, then we ask that you identify the measures you think are necessary for the application to be placed in an approvable form.

Option No. 4, tabling. In rare circumstances, the panel may decide to table an application. Tabling an application does not give specific guidance from the panel to FDA or the applicant; thereby, creating ambiguity and delay in the process of the application. Therefore, we discourage tabling of an application.

The panel should consider a non-approvable or approvable with condition recommendation that clearly describes corrective steps.

If the panel does vote to table a PMA, the panel will be asked to describe which information is missing and what prevents an alternative recommendation.

Finally, following the vote, the chair will ask each panel member to present a brief statement outlining the reasons for their vote.

DR. SWAIN: All right. Thank you.

Now, let me remind the panel that we are an advisory panel and there is one single page, both sides, of questions that the FDA have come up with. So, in our discussion of this product, there are, I think, 12 questions -- forget about the future developments of TMR -- but 12 questions that we really need to address.

So, what I would like is --

DR. STUHLMULLER: I guess by policy the company -- the sponsor needs to step back from the presenting table.

DR. SWAIN: Take your seats if we can find seats. Hope there is enough seats or scoot the seats back. That would be easier.

Anybody can lead off the discussion, primary reviewers, secondary reviewers.

DR. CALIFF: Well, this has, obviously, been a difficult session because of the tremendous need identified for these patients. I think the concerns that have been raised really fall very much in the fundamentals of clinical trials and I would like to have some discussion within the panel about how far afield of fundamental clinical trial methodology we can go and still feel comfortable.

I am very uncomfortable when -- you know, we talk about missing 10 or 15 percent of a primary endpoint as being a major problem in clinical trials and here we have got over 50 percent of the primary endpoint missing. We have got a secondary endpoint, which is based on a subjective evaluation, for which no effort has been made to obtain an unbiased estimate from the interviewer in the face of multiple publications and previous studies that have employed such methodology to try to achieve an unbiased estimate of functional status in an unblinded study.

Then you have got this huge crossover rate, which understanding the desire of the clinicians to help the individual patient. There is a counterbalancing ethical issue that I just want to raise that I think -- and I would

also like to understand better from the point of view of the panel and that is the ethical imperative when a patient volunteers for a clinical trial to achieve a clear answer to the question so that the experiment is not done to no avail.

This question of whether the crossovers really had to occur -- because in my mind, for example, the mortality, I have no way of really estimating the safety of the study, of the procedure, when 18 of the deaths occurred after the procedure and six of the deaths occurred without the procedure, you know, in the facing of a crossover occurring without information about what really precipitated the crossover in the first place and in the face of adverse event data showing a threefold increase in the first 30 days in heart failure and these arrhythmias.

So, I am very troubled and concerned and would like to get some input. I regard these as very fundamental aspects of how clinical trials are done and worried about how far we can go in this kind of methodology.

DR. SWAIN: Dr. Ferguson.

DR. FERGUSON: I would like to ask a question of, I guess, the cardiologists on the panel because I never

questioned in my mind when I read through here the fact that every patient who crossed over needed to cross over. They were in the ICU for seven days on drips with unstable angina even on IV drip. I mean, isn't that an indication that something needs to be done?

It has been standard form that way before. Or have I missed something?

DR. TRACY: I think one clue to that is that at one point, if I am reading the data right, there was an observation that too many crossovers or a high percentage of crossovers were taking place and at that point, it was instituted -- a six month wait period was instituted. So, that would suggest that those crossovers may not have been necessary.

DR. FERGUSON: But the protocol says that the criterion for crossover was seven days in the unit.

DR. CALIFF: Well, I would make two points about that. I think the first is of the presumption and the, quote, something needs to be done category is that you are offering the patient a therapy, which is known to be beneficial, when, in fact, if you are willing to randomize

the patient into a trial, the presumption is that you don't know that the treatment is beneficial.

That is why you are doing the trial, because it is not known whether the treatment is beneficial. So, I think there is a tokology(?) or -- maybe that is the right word -- there is a problem with that logic in that you are doing an experiment on an unknown treatment and then you are arguing that the patient has to have the treatment because it is going to be beneficial.

And the second thing is we are all familiar with the concept that --

DR. FERGUSON: We have been doing that with coronary artery bypass for 25 years.

DR. CALIFF: Well, I would argue that there are some well done randomized trials with coronary artery bypass that show that it is a beneficial procedure.

DR. FERGUSON: There are now. But I am talking at the beginning of the --

DR. CALIFF: Right. Well, what I come back to in the end is that it is interesting that the primary sample size calculation shows a need for 12 patients per group well

studied and the question is is that asking too much to get definitive data on a very small number of patients, which might be able to be done very quickly.

But I am anxious about this and very interested in other's opinions.

DR. SWAIN: Dr. Weintraub.

DR. WEINTRAUB: I guess I have to ask the question looked at from the other end. If the device is not approved or if it is postponed in some way, I sort of have to ask the panel what data would you like to see developed, let's say, over the next year that is going to change your mind in a practical way. I am not talking about what you would like in terms of the ideal clinical study. But I think one does have to realize that these are patients without much of an alternative and it seems to me the sponsors have made a reasonably good faith effort to get data.

The reasons they were not able to were listed. You can buy them or not buy them, but they were at least accounted for. Do you think that that really is going to change very much or is that any of our business?

In other words, I am asking the question, if one

pushes this over, if one decides that the data are not sufficient, will we ever get sufficient data, as you define it in your mind, given that these patients are patients who have no -- very little alternative?

DR. CERQUERIA: Well, I would like to make a couple of comments.

We talked about two problems with the data and if we use the profusion data as an endpoint, the quality of the initial data, I think, was an issue and we identified some better methods of analysis, a quantitative method of analysis. And I think with quality control of the equipment that is used so we can get a quantitative, more reliable measurement of the profusion defect, I think it would be important to do that.

Then the other problem was the data dropout and I think we really have to look, can we get adequate information baseline, three months, six months, twelve months? Can we get two of those and make a concerted effort to get it in these patients in a more rigorous way than what was done in the protocol?

I think those two things would help shore up the

validity of the primary endpoint, which was chosen, which was the profusion data. I don't think that was done so far in the data that has been presented and I think it can be done in a meaningful way.

You are still not going to get a hundred percent of the profusion data, but I think you will get closer to 70 percent, 80 percent, and some of that occurring -- the data that you don't get will be in patients who died or had other events.

DR. TRACY: A question that comes up sort of as a corollary to that, I have the sneaking suspicion that even if we had more nuclear data or more PET data, that we wouldn't have the etiology of improvement. So, can this device be approved without our understanding the mechanism by which anginal improvement occurs?

I think they could have had better compliance and they certainly should have had better compliance with all aspects, both on the angina assessment and on the different profusion methods that were chosen, but I don't think that they discovered the mechanism by which their device works.

DR. SWAIN: The question is can -- we are deciding

safety and efficacy. Can you decide the efficacy without an understanding of the mechanism?

DR. TRACY: Right.

DR. SWAIN: That is the question. Any answer to that?

DR. PARISI: I think you might be able to if the mechanism were unequivocally clear cut because all the studies came out one way and it showed that -- no one disagreed about the degree of profusion. I think the problem comes is that there are a number of patients who either didn't change or who were worsened by the profusion study and, yet, whose angina got better.

So, the mechanism is obscure and, yet, the data seems to suggest that patients do get relief of angina. I guess I am bothered by the fact that we have questionnaires which can be self-administered so that presumably there is a contact with the patient since you determine vital status.

Now, why can't these questionnaires that are self-administered be self-administered and just get the data in, at least from the questionnaires? I am sort of bothered that a third of the data on something that can be self-

administered is out at six months and, of course, we haven't reached the one year point in a lot of the patients. So, we don't really know much about that in the randomized trial.

DR. EDMUNDS: I guess I will sum up my thoughts.

First of all, the company has a very difficult burden in this group of patients, who most of them have been operated on before. I assumed all have three vessel disease, but there is -- they have identified a cohort with a mean ejection fraction of only moderate left ventricular dysfunction. This is quite different from the cohort that all of us have seen, who do this kind of work and which the ejection fraction is between 10 and 15 or 20 percent and you have a chronic Class 4 or Class 3 angina.

I think there is no doubt to my mind that this study, there are problems, serious problems. It is a randomized, unblinded study in terms of the overall management of the study, in other words, compliance with the investigators, consistency of the data collected, data loss, crossover and the evaluation of angina.

I haven't touched about the profusion studies yet because that is even more serious to my mind because they

are discordant with the relief of angina. And I think the company has to realize that all of their stress or their profusion data, except for the PET, is discordant with the relief of angina.

Now, the follow-up is too short. You only have six months data and we really could use that 12 month data if you had it. There is no mechanism, but the company does not have the burden of the mechanism, as I understand this process. So, I am torn because I think you have demonstrated that the procedure relieves the symptom of angina.

The trouble is the history of angina is replete with episodes of the relief of angina by some intervention; the Beck 1, the Beck 2, the Vineberg and so on down the list. It is a potholed history, if you will. What is very hard for me to understand, is this another pothole or is this something -- is this an advance?

If you could show vessels, that would be an advance. If you could unequivocally show that your profusing miocytes(?) and they are metabolizing, as Bud's PET data show, but even that has to be rigorously looked at

because you need to see the hybrinating myocardium and identify that. But I am not at all sure these holes were drilled into hybrinating myocardium.

I can offer at least five, maybe six, mechanisms for the relief of angina that are independent of revascularization of the dead meat or the hybrinating meat.

So, this is a very, very difficult thing for the company but it is also very difficult for somebody coming in and objectively evaluating it. The randomized, controlled, unblinded trial is a best effort, probably, to deal with this, but because you have had difficulties with that, we can't act sympathetically to your difficulties. We have to represent the public and in so doing, we have to ask that you meet the standards that the public has asked for.

So, I am very convinced that the procedure relieves angina. I am not convinced that it profuses miocytes.

DR. SWAIN: Dr. Wittes.

DR. WITTES: I think there is also another issue that reflects what Dr. Califf was referring to. It is not clear from the way the data are presented what the down side

risk is. We are seeing these -- the mortality story is difficult because of the crossover and I find the tables of the non-fatal adverse events very hard to read because you can't tell which are clusters of events and which are individual events. It is hard to measure. It is hard to see overall what the risks are. I think it would be important to put that together in a coherent and interpretable way with longer follow-up.

DR. SWAIN: Dr. Sethi.

DR. SETHI: I would like to make a concern. Number one is it appears to at best six month study, at best, probably less than that.

The second concern is that one of the endpoints of the angina, which we are all talking about, you know, that is what appears to be that this device improves angina. But the angina was evaluated by different sources, by the nurse, by the doctor, by surgeons, by radionuclide doctor, by I don't know who else, self-administered test.

So, I am very concerned about how the angina was evaluated and that is one of the very important points here.

DR. WEINTRAUB: I am struck by, number one, the

FDA statistician's review, which suggested that if you look at the symptomatology, the angina, it is very clear that the device is effective. If you look at page 431, the comparison of the symptoms of the thallium for the Phase 3, looking above the line, that is the -- there are none, zero, patients that were worse from the symptomatic point of view. That is zero.

If you turn the page over and you look at the comparison at six months for the controls, there was only one, two, three that were improved symptomatically compared to all the others. Now, one can argue about bilateral mammary ligation, the Beck 1 and Beck 2, all of these. I agree there are a lot of pitfalls. But none of those previous studies, to my knowledge, were ever randomized with controls.

This does have controls. It is not ideal. It is not totally consistent, not at all consistent in terms of the reprofusion data, but the reprofusion data I would question in a lot of different studies. It is very inexact. There may be microvascular connections that we can't see on reprofusion. Certainly, there may be other reasons why it

doesn't tally, but I don't think -- you know, I don't think that is critical.

Certainly, such data that is there, although it is inconsistent, on the mass shows that there is an improved vascularity.

DR. SETHI: I would like just to correct you that there was a randomized study between medical treatment and implanted mammary artery implantation in late sixties or late seventies and it was definitive that IMA implantation in Vineberg patients did not improve better than medical treatment.

DR. EDMUNDS: Ron, I would like to point out through no fault of the FDA nor of the company, this study wasn't really controlled. The control group of patients had medical therapy but they did not have a cut on their chest. Okay? And it is that placebo effect of the cut on their chest that is a major concern.

Let me finish. Now, I don't know the way around that and that is why I am uncomfortable and feeling a little unfair. But the fact of the matter is it is true. This is not a controlled study in the strictest context of the word

because the patients -- the control patients did not have a cut.

DR. WEINTRAUB: But it is as controlled as it can ethically ever be. There will never be a controlled study with a cut on the chest.

DR. EDMUNDS: We have to interpret the data we have and we have to factor that into it.

DR. SWAIN: Dr. Tracy.

DR. TRACY: If we are trying to look for an endpoint by which we feel the procedure is safe, I am going to need help from the statistician to understand the mortality data, which I thought I understood before I came in here, but now I am sure I don't understand.

If we just think about the mortality data, can we find an endpoint there? Because I remain concerned about arrhythmic events.

DR. SWAIN: Dr. Wittes.

I guess the question is we are dealing now with not efficacy but safety.

DR. WITTES: I know and that is what I am confused about. That is one of the reasons I made the comment I did.

I am also confused by the mortality data. I still don't understand where the deaths occurred in relation to the TMR and it is very hard to interpret crossover data because crossovers are presumably those people who are going for salvage therapy. So, you never know whether they are, therefore, at higher risk for that or they are at lower risk because people think they are going to survive the procedure.

It is very hard, but I -- it would be nice to have seen some -- more of a relationship between the surgery and the event and also more of a relationship between what happened to these life-threatening arrhythmias. Did they eventually -- did these people eventually die? I don't have a sense of the trajectory of their lives and it may be partly because we are talking about some of these patients didn't even have six months of follow-up.

So, I am feeling that there is not really enough here to answer that.

DR. SWAIN: Dr. Vetrovec.

DR. VETROVEC: I have been involved in a number of anginal medical trials over the years and I can't believe

that today a medical -- a new medical therapy for angina would be approved simply on a reduction in symptoms without some other endpoint.

DR. CALIFF: I want to keep hammering on the crossover issue to make -- because there seems to be some discordance. It leaves me, first of all, very unsure about the mortality because -- and, Larry, actually you may be the best person to -- you have been doing these kinds of trials that involve revascularization for a long time.

How do you interpret it when half the patients have crossed over and two-thirds of the deaths occur in the patients who crossed over? Can you really know what the safety of the procedure is under those circumstances?

DR. SWAIN: Dr. Friedman.

DR. FRIEDMAN: No, you can't interpret it. The answer is that when you have a study like this, I wouldn't say that it is the same as having no study, but it is pretty close. This is really not a controlled study because you can't say we have two groups that are -- that were randomized and, therefore, they are a priori comparable. You have to look at it in a variety of other ways.

Well, here, unfortunately, the data don't even allow us to look at it in a variety of other ways because not only is there the crossover, but even in the absence of the crossover, you have so much incomplete information. I can understand having incomplete information for the profusion. Well, it is difficult.

I just don't understand the degree of incomplete information for the angina even, which is -- and it makes me nervous. Yes, I know you can play, you know, worst case/best case scenario and still come out with some -- but the fact that it is so incomplete makes me question the whole concept here.

So, you know, that was a long-winded answer to your question. I just don't think that these data allow us to come up with any kind of meaningful answer and certainly for adverse effects, there is not much you can do at all here.

DR. SWAIN: That is the -- I think, to talk about what Dr. Weintraub is talking about, I don't think anybody is suggesting sham operation. That is not ideal. We are dealing between ideal randomized study with complete data

and minimally acceptable quality of data in this particular study. That is, I think, what we have to judge on.

Do we have a minimally acceptable quality of data to make a decision about safety or efficacy?

Dr. Wittes.

DR. WITTES: Maybe one of the things that is troubling is that the data are so good. I mean, what you see is this very, very dramatic difference in the face of a lot of missing data. I think that is sort of what raises for me the question, is there -- see, I am much less worried about the placebo effect in general. I mean, if there is a placebo effect, so there is a placebo effect. If there were -- if you could save lives by giving people an operation that they didn't need, well, that is not so terrible.

But if what is going on is something much more subtle, that people who are willing to answer this form are people who are overreporting how well they are doing and so that there is something about an interaction between answering and the kind of discussion that we heard over here and feeling really good about having had the surgery and that explains this very, very dramatic effect that we are

seeing in the context of nothing coherent, no concomitant effect on the profusion and nothing in the mortality.

That is, I think, what leaves me --

DR. EDMUNDS: Well, I think we have to admit that despite all the problems that have been enumerated, that if we understood the mechanism by which this treatment revascularized the treated myocardium, we would probably have very little reservation. But we don't understand the mechanism and lacking that, we really can't even deal with the relief of angina issue.

DR. SWAIN: Dr. Califf.

DR. CALIFF: I just want to voice one note of disagreement with what you just said because it would be great to know the mechanism and it would make me feel better, but --

DR. EDMUNDS: Not good enough, huh?

DR. CALIFF: -- cardiovascular disease is replete with therapies, such as vasodilators for heart failure, autotrophic agents for heart failure and arrhythmic drugs that have very plausible and actually physiologically verified mechanism of transient improvement that end up

increasing mortality in the long run.

So, the mechanism, to me, is very helpful but not sufficient. We need evidence of clinical benefit.

DR. EDMUNDS: I don't disagree with you and I think you know that, but I do think that if we had the mechanism, we would be able to --

DR. CALIFF: It would put us at peace.

DR. SWAIN: Any other -- Dr. Parisi.

DR. PARISI: You know, in all fairness, in the original studies on coronary bypass surgery, we really didn't have survival data until we got out until several years, so that this procedure went on with relief of angina really as almost self-evident.

So, in some respects, if -- but the data wasn't as incomplete, I think, as this data is. That is one of the problems. It is incomplete in several respects, the duration of follow-up for the patient population relative to what was said would be done and then finally the aspects, which really haven't been touched upon; cessation of -- all the things, which would really just clean it up to reassure us that other things weren't going on in these patients who

have the surgical procedure.

So, I think there is additional incremental information here, which would put my mind at ease, at least in the historical context of this study relative to, say, the early VA studies.

DR. SWAIN: Dr. Casscells.

DR. CASSCELLS: I think all these points are very helpful. I want to be sure that we don't penalize a company and a group of surgical investigators for conducting a randomized trial, which is rare in surgery and I want to applaud them for that.

I suspect that there is a use for this device, but the data is woefully incomplete, all the points that have been made before. I suspect, when they -- if the company can get the data on the current patients or get more patients, we will find that there is a benefit in the lased segments that exceeds the benefit conferred on the non-lased segments that come from compliance and lowering the cholesterol and what not.

Interestingly, one of the benefits is that when you lower cholesterol, you permit angiogenesis. One of the

main causes of angiogenic failure is a high cholesterol. But there is some benefit, I think, here, but we certainly can't prove it.

And the question is do you vote "yes" because there is probably a benefit or what is the level of confidence that you need as a doctor to recommend it, as a citizen or patient to undergo it? I think the level has to be a little higher, the level of confidence, in light of two things.

First is all the biases that we have. We have got to be so careful. We want to help the patient. The patient wants to be helped. Some people have reputations and jobs at stake. So, we have to bend over backwards to be sure that the data is as clean and clear as it can be.

This is a 2,000 year old problem in medicine. You know, Galen, the famous Roman physician said -- of one of his early therapies, said "Half the people were cured and half died." Therefore, the therapy was effective for all but the incurable.

So, we have to be very, very careful that we are not dealing with this kind of unconscious bias that can

creep in. And I know the integrity of these investigators and it is sterling, but little biases creep in. So, I want to encourage them to collect this data.

I predict in the end there will be some use for it. It is not a life-saving device and there is no immediate hurry.

DR. SWAIN: I was actually going to ask a question. I think Dr. Casscells has given me his answer. The number one question from the FDA to us is do we have enough data in this submission to evaluate this device, safety and efficacy, in any population. And that is probably what the vote -- all the other stuff is really secondary -- what the vote will hinge on.

Does anybody else want to address that particular topic?

Dr. Ferguson.

DR. FERGUSON: I think in fairness, there are two things that have come out here to me, admitting all of the things that have been brought up, which are all correct, both statistically and medically and so forth. The things that I need somebody to tell me as a freshman here is that

it sounds to me like the company has acted in good faith in terms of what they have done. Now, I agree that they don't have enough data and maybe that should have been picked up by them and they should have said we want to get a hundred more patients.

But they were acting, it seems to me or at least what I hear, in faith in terms of what endpoints were defined. They brought those, as I understand -- I am asking for information really -- they brought those endpoints to the FDA and the FDA said these are fine and you can proceed with your study. Then the number of patients was the other issue.

That is one point that I would like to hear somebody describe. The second point, Julie, is I come back to the point that we have spent a lot of time talking about the patients, the small group that died. We have talked a lot about the flaws in the data, which, again, I agree with, but I mean this procedure has been out there a long time. I mean, as a surgeon, I have been listening to papers about this and listening to the results and they come, as you say, from sterling investigators, every one, every place.

I would like to know what the panel feels about that because we haven't really talked about that group of patients, whose angina has been relieved and who are continuing after year after year to be relieved. I mean, it is not like we stopped that study at six months or a year.

DR. SWAIN: Let me ask Dr. Callahan to comment on the FDA, only from the panel perspective, as a member for the last, I guess, seven years or so. You know, we have to judge on what is presented to us. The history of who said what to whom is probably irrelevant.

Is it safe and efficacious for patients? Then, Dr. Callahan will comment about the FDA's involvement in this.

DR. CALLAHAN: With the caveat that the staff can help back me up if I misquote something.

Our Clinical Trials Board had looked at the data, when the angina data came in and said that we would like to see one year's profusion data. So, that is where the FDA came in and started suggesting things. We have an obligation to allow trials to go forward if they look like they are going to collect reasonable data.

Now, it is up for you to judge whether -- I have heard some comments from Dr. Ferguson saying that these were the -- that the company performed in good faith. They did perform studies but you will have to judge how good a faith that they adhered to the study protocol as defined.

FDA did comment. We allowed the studies to proceed. We basically try to guide these studies as they go along, but we, as you, wait for the data to come back in again before we make any final decisions.

Maybe I will just stop there. I don't know that I need to say any more.

DR. SWAIN: Dr. Califf.

DR. CALIFF: I just want to comment about the sterling investigators. I think it is true in this case, but, you know, all you have to do is to think back to quinidine and flosequenon(?) and a number of other therapies studied by excellent, very bright people in good faith and we simply have to let the data speak for themselves.

After all, it is not the investigators that are determining the outcome of the patients. It is really the effect of the treatment. So, I don't think this is a

statement about the investigators or the critique. It is more the question of do we have adequate data to really know the effect of this procedure on the outcome of the patients.

DR. SWAIN: Dr. Wittes.

DR. WITTES: I don't think it is an issue of another hundred patients. I think that there are -- this is a 200 patient study and there could be data collected from these patients. I think the power could be adequate in this study.

DR. CALIFF: Do you think that is true even with the crossover rate?

DR. WITTES: Well, the analysis will be tough. I don't know. I don't know how to deal with the crossovers.

DR. SWAIN: Yes, Dr. Tracy.

DR. TRACY: I think it is just -- it is difficult. I don't think that they are ever going to improve the mechanism. I mean, I think the mechanism is going to be under investigation for the next ten years, but there must be data that is close to being available that would explain whether this thing is harmful or helpful.

We have got animal data showing fibrosis. We have

got sudden death. We have got no apparent alteration in the overall mortality. We have this ambiguity in the -- you know, the 12 people who went here and these guys went there. Some of these things can probably be readily sorted out, I would think, without having to ask them to reinvent the entire study to come up with a mechanistic explanation.

DR. SWAIN: Dr. Parisi.

DR. PARISI: Yes, i think that the study might be salvageable by getting one year data in a uniform way by approaching all the investigators and training whoever is going to collect one year data on angina status that do it according to the standards you would do in a drug trial and since you declared you were going to do the nuclear studies, to get as much of that as you can, at least to show there is no major deviation from the data you have had today.

I think those points will be salvageable. The crossover and its effect on mortality, I don't know. I would have to defer to others.

DR. SWAIN: I think probably the two things we are talking about is whether the study design was adequate. I think I heard that it probably was. And then the question

is was it then carried out to minimally acceptable levels.

Any other comments? Dr. Vetrovec.

DR. VETROVEC: I think it is very favorable that it relieves angina. The thing that worries me, though, is that in the patients -- and the crossover data is important -- the patients with 50 percent or greater ejection fractions, they may be terribly troubled by angina, but they are likely to live. And if this therapy somehow really affects mortality in low risk patients, we need to know that, I think.

DR. SWAIN: Another safety question.

If there is no further discussion, would -- Dr. Weintraub.

DR. WEINTRAUB: Yes. I just want to ask a question. We had, as I recall, a somewhat similar situation back a couple of years ago with a certain stent and the issue at that time was data collection. As it turned out just serendipitously there was a large randomized study just about going to be reported at the American Heart, I think it was at that time, and the panel turned down the stent but then with the proviso that as the new data became available,

which we knew it would, that rapid reconsideration would be looked at.

My sense of what is going on here is that that type of thing might be appropriate. I certainly understand everyone's concern. I have my own concerns about the adequacy of the data. At the same time, we are all dealing with patients and in this case with patients who don't have much of an alternative. I have referred a small handful of such patients for laser therapy and they have been patients that just are at the end of the road symptomatically.

I don't think it would be right to withhold that potential therapy from patients while we wait the development of new data over three years. So, I am just asking if there is some way that if the panel decides that further -- more complete data are required, that this can be looked at fairly quickly as the data are developed.

DR. SWAIN: I hope the ones you referred went into a randomized trial. That is the hope.

Dr. Casscells.

DR. CASSCELLS: Just very briefly, on this issue of feeling desperate to do something for desperate patients

is one we all encounter. We have to remember that there are thousands and thousands and thousands of patients who have been studied with unstable angina. The mortality is between 4 and 20 percent. The groups are very, very, very well-defined. Dr. Califf can speak to this better than I can, but as Dr. Vetrovec said, with an LEF of 50 percent, even with resting ST depression, more or less continuous pain on drips, I think we would not have in our center 18 percent death rate with unstable angina. That is what we had in the crossover. So, we need to be careful about compassionate use arguments.

I think, as I said before, I think there is going -- there will probably will end up being a role for this thing but we have got to be very scientific about it.

DR. SWAIN: If there are any other comments -- someone is going to have to make a motion. There are three possibilities on motions. Approve it, approval with conditions or non-approval, not disapproval, non-approval.

DR. CALIFF: I guess I will make a motion for --

DR. SWAIN: This is Dr. Califf.

DR. CALIFF: I will make a motion for non-

approval. I guess we are supposed to discuss the reasons why later.

DR. SWAIN: Is there a second to the motion?

DR. SETHI: I will second that.

DR. SWAIN: Dr. Sethi seconds it.

Discussion. I guess everybody is a little tired here. It is amazing. No discussion for this group after that. I am not complaining.

DR. CALIFF: Do we need to go through the reasons why or is that a later --

DR. SWAIN: I believe that one doesn't need to do that now, but one certainly needs to do that -- this group needs to do that if that, in fact, is the vote. No matter what the vote is, there needs to be a discussion of follow-up and all that.

Any other discussion? The motion on the table is for non-approval of this device and it has been seconded.

Any other discussion?

[There was no response.]

Then we will vote and I guess everybody except for the -- actually, Mr. Jarvis, do you have any further

questions? I am sorry.

MR. JARVIS: No.

DR. SWAIN: Except for I think two on the end and one on --

DR. VETROVEC: Can I ask him to at least state his major reasons for non-approval?

DR. CALIFF: We are asked to judge based on evidence for safety and efficacy presented in the briefing and that comes out in this hearing. I am hopeful about efficacy but feel that the standard of data, quality and completeness is a standard that is too low to be served.

If we can tell people they can collect less than 50 percent of the primary endpoint in a clinical trial and that that is an acceptable standard, I don't know what would be unacceptable.

With regard to safety, the crossover issue has left me very concerned that there may actually be an excess mortality in this relatively low risk mortality-wise group of patients. With an EF of 50 percent, we have got a substantial mortality and most of the mortality in the control group is actually in patients that had the

procedure, two-thirds of it.

So, I am hopeful and, you know, I have got a close relative that needs this procedure. So, there is nothing I would rather do than see data that would be convincing, but it is -- it doesn't meet the standard that I think we have been asked to go by, in my opinion.

DR. SWAIN: Further discussion?

[There was no response.]

Then we will call for the vote. I think we will do this as a roll call today. Important topic. So, let's start with Dr. Tracy and Dr. Stuhlmuller will record this.

DR. TRACY: I agree with non-approval.

DR. SWAIN: Dr. Vetrovec.

DR. VETROVEC: Non-approval.

DR. SWAIN: Non-approval? Could you speak into the -- we are recording this.

DR. VETROVEC: Non-approval.

DR. SWAIN: Dr. Wittes.

DR. WITTES: Non-approval.

DR. SWAIN: Dr. Parisi.

DR. PARISI: Non-approval.

DR. SWAIN: Dr. Califf.

DR. CALIFF: Non-approval.

DR. SWAIN: Dr. Swain -- non-approval.

Dr. Edmunds.

DR. EDMUNDS: Non-approval.

DR. SWAIN: Dr. Casscells.

DR. CASSCELLS: Non-approval.

DR. SWAIN: Sethi.

DR. SETHI: Non-approval.

DR. SWAIN: Ferguson.

DR. FERGUSON: I disagree with the motion.

DR. SWAIN: So, you disagree with non-approval.

DR. FERGUSON: Correct.

DR. SWAIN: Dr. Weintraub.

DR. WEINTRAUB: I disagree with non-approval.

DR. STUHLMULLER: I need to make one point. Dr. Swain as the acting chair only votes in the event of a tie. You are deputized in the event of a tie.

DR. SWAIN: So, it is two against the motion. Dr. Weintraub and Dr. Ferguson. And nine for the motion. That is carried.

Now, we need to go through each member of the panel, including the ones that voted against this motion and say what you would think. Let's start with the people against. Do you feel that anything else needs to be done in the study or it is fine the way it is?

Dr. Weintraub, what would be your recommendations?

DR. WEINTRAUB: Well, my recommendations would be to take the cohort that is -- that is, the roughly 200 patients in the cohort and complete the data insofar as it is possible on that cohort. I don't think collection of further patients is necessary probably.

DR. SWAIN: Dr. Ferguson.

DR. FERGUSON: I essentially agree with that. I think non-approval puts this back a number of years; whereas, if we just approve conditionally, we can ask for all the data that we want for them to continue to collect, as I understand.

DR. SWAIN: Dr. Callahan, I think, can clarify that issue.

DR. CALLAHAN: I think as was pointed out by Dr. Califf, we are a data-driven organization and we --

certainly if you can spell out in detail the exact data that you want and it was imminent, as it was in the Palmar-Schatt(?) stent trial -- in other words, we were aware that the studies were out there -- but if you have a list of conditions that is a mile long that you need, then that is where we separate.

DR. EDMUNDS: That was my reason for voting for non-approval.

PANELIST: Point of order. A vote of non-approval at this moment doesn't mean that they can't come back later, does it?

DR. CALLAHAN: No, that is true. They can come back.

PANELIST: They can come back with the same cohort of data and more data, hopefully, but it doesn't mean that they start from square zero.

DR. CALLAHAN: Not at all, no.

PANELIST: I think that is an important point.

PANELIST: But they don't move as fast as if we do the fast track.

DR. EDMUNDS: Is there any data to show that a

non-approval vote decreases the speed with which they can come back?

DR. CALLAHAN: No. In fact, for the one that was mentioned by Dr. Weintraub, just the opposite. It came back within six months with the appropriate data. So, we are data-driven. So, whenever the data is there, we are willing to act on it.

DR. WEINTRAUB: I would just urge a relatively expedited review, assuming they can get the data.

DR. CALLAHAN: This has been an expedited review. This submission has been expedited.

DR. WEINTRAUB: An expedited re-review.

DR. EDMUNDS: Well, I will confess first. I guess this is what -- but I could not vote for the other two choices as defined on the basis of the flaws in the data collection here and the fact that the evaluation of angina pectoris at best is always very difficult and subjective. And I reject the idea that there was no alternative because people with an ejection fraction of 50 percent can go on and have their infarct and get rid of their angina and many do and they don't die.

I do think that the sponsors would be very wise to correlate their ejection fractions more closely with their morbidity and mortality because I think that is where it is and if we could ferret that out, then I think it would clean up their data a good deal and probably in favor of their position.

DR. SWAIN: Dr. Edmunds, so your specific suggestions? Complete the data.

DR. EDMUNDS: To what degree do I have to design the study sort of on the run? I mean, I can't do that not when good people have given a great deal of thought to it, but I think that probably the concerns about safety are probably wrapped up in the ejection fractions of the patients who died and may be independent of the treatment.

So, I am very hesitant to blame the treatment for any perceived changes in mortality. I don't think there is any -- they have shown any difference in the mortality. I do think that they have shown that the treatment relieves the symptom of angina in the greatest number of patients, despite the flaws and the reservations that have been stated.

But I am very troubled because of the history of angina and the lack of a mechanism.

DR. SWAIN: Dr. Califf.

DR. CALIFF: I might throw out a proposed set of data and then I have still a question.

I would certainly be pretty satisfied from the efficacy point of view if there was an assessment of each of the remaining living patients by a trained interviewer with a script that instructed the patient not to identify what the treatment had been during the interview and then went through a structured interview to assess angina status and quality of life.

I think there is plenty of room for angina improvement when we don't know the mechanism being an important issue and in that same structured interview, which would probably take about 20 minutes per patient. It could be done by telephone. One could also ascertain the risk factor data that Dr. Casscells is interested in.

I am personally less interested in that, because I think it probably is going to be equally distributed into two groups, but for a minimal incremental amount of time and

cost, that data could be obtained, I think, very quickly.

With acceptable completeness of follow-up, that would resolve the efficacy issue for the endpoint of importance. I am personally also much less interested in the imaging data, but I think others would ask for that. But it still leaves me unsettled about the safety issue and I would really appreciate more discussion about what an acceptable approach to the safety issue would be.

DR. SWAIN: Dr. Wittes, do you have a comment about whether this is salvageable from the safety standpoint, considering the number of crossovers?

DR. WITTES: Well, actually, the crossovers -- the early people crossed over, but the people that were entered later didn't cross over for at least six months. Now, I don't have a sense of how many that was.

I also don't know -- these tables, these figures, like on page 108, when was that done, how long ago was the three month person -- did a three month person show up in this table? Is it already -- has that person already been followed for nine months? Because it may very well be that if everybody could be followed for 12 months and the subset

of those whose crossover couldn't occur until six months is a large proportion of the people. I don't know that that is true, but if it were, then I think, looking at that group and it is 12 month mortality might tell us a lot about -- or comfort us that what we -- the apparent increase in mortality is just noise, early noise.

DR. CERQUERIA: I would like to comment. I am still a little bit bothered by the EF data. We actually looked through some tables and in the 14 patients who died, the average EF was 45 percent and in the other patients it was 50 percent. I think that data, we never did find out how the EF was determined. Was it cath? Was it echo? Was it radionuclide? It would be nice to have good information on that EF.

I think they really need to try to -- they have all the data. It was translated to profusion data using -- and to do quantitative analysis. That would still be possible and I think, at least in the patients that are alive, if they could try to get the 12 month data, make a real effort to get that, you would at least have -- everybody has a baseline and you would have 12 months. You

are missing some intermediate points, but I think that would be useful. Quantitative method, complete 12 months on at least everybody and I think try to get good -- the EF data still bothers me. Those EFs are too good for people that are dying, especially if they have had all those big profusion defects. I think that would help clean up, at least without acquiring additional patients.

DR. SWAIN: Better concordance. Was it you that mentioned or somebody about a core lab for seeing what the baseline coronary disease --

DR. VETROVEC: I mentioned that.

DR. SWAIN: You mentioned that. What -- do you feel that that needs to be looked at to know that we are comparing apples and oranges?

DR. VETROVEC: It might very helpful to know what the risk factors were anatomically for these patients. That might help you define much better whether the deaths have relevance based on some standard things that you know about extent of myocardial risk by other methods than profusion.

DR. SWAIN: Dr. Sethi, do you have any other, besides what has been mentioned, suggestions?

DR. SETHI: No.

DR. SWAIN: Dr. Casscells? Dr. Edmunds? Calif? Any other --

DR. EDMUNDS: Well, one.

DR. SWAIN: Dr. Edmunds.

DR. EDMUNDS: If it is possible, I would -- the PET data, I think, would be very valuable at 12 months, controlled, treated. How you would arrange a sample of both and be realistic about cost and so on, I think are big issues.

DR. CERQUERIA: I would have some concerns. I mean, you only have baseline data on, I think, 16 patients, so you are going to have a small, limited number of patients to look at. I would be concerned that it is too small, from one center only and it is not going to be reflective of the rest of the patients.

DR. SWAIN: Dr. Wittes.

DR. WITTES: Also, I would urge that there be some prespecification. What we are asking for is collecting data. We all know the data up to now, but let's have -- if there is a 12 month endpoint, that the angina and whatever,

imaging is done and so forth, that how that be analyzed be specified up front.

DR. CASSCELLS: Just to follow up on points that Dr. Tracy and Dr. Vetrovec made before, this issue of silent angina ought to be addressed somehow, either with treadmill tests looking at the timing and degree of SD segment depression or ambulatory Holter(?) monitoring. It is an important issue these days and I think that ought to be on the list.

DR. SWAIN: Okay.

Dr. Weintraub.

DR. WEINTRAUB: Just a question of the sponsors.

Do you have any idea at all about the percentage of patients at baseline that might have had exercise tests?

DR. LEFEBVRE: It would be very low.

DR. WEINTRAUB: Thank you. Or I should say what percent would have had dipyridamole testing of any sort; that is, any kind of stress testing?

DR. LEFEBVRE: 100 percent.

DR. WEINTRAUB: Had stress testing?

DR. SWAIN: Yes.

Dr. Parisi.

DR. PARISI: I think also it is very important that there be a uniform effort to collecting any one year data. If I understand the situation correctly, you reach the one year point on all these patients this September, which isn't too far off. So, you would have a one year or greater follow-up on every patient who is randomized and accessible at that time and I think there needs to be, as Dr. Califf suggests, a very uniform approach to interviewing these patients, which is consistent from center to center.

I think also the nuclear data up front should be collected in a uniform way by training of technologists when these patients are brought in, so you don't have to then admit them to a core lab that throws out a lot of the data.

That may have some bearing on this angiogenesis theory, at least, in terms of the data starts to move progressively in one direction, which it may or may not. So, I think those are important.

Now, the other thing is that as I remember the data, the patients who had unstable angina, who got this procedure, who weren't in the randomized trial, had a very

high mortality and it is possible that the context of this mortality needs to be defined. In other words, if a patient comes in and has unstable angina and can't be weaned for a week in an ICU and gets a TMR, that is different than a patient who has more frequent angina and crummy looking vessels.

So, I think that that might be a way of looking at the mortality at least with an asterisk down the line if you get more patient information.

DR. VETROVEC: I would first of all hope that somehow all the work that has gone into this, which I think is -- was a reasonable concept, could be salvaged. The suggestions by Dr. Califf, I think, for the one year good follow-up sort of independently would be, I think, excellent.

The mortality issue is probably what bothers me the most and I think that the first thing to do is to really look at every death and try to analyze it from all the ways that we have talked about for risk factors and see if something can't come out of that that will give you insight into explaining that. That would help me tremendously if I

understood that better.

I am just worried that there is a -- we haven't answered the question of whether non-high risk patients are put at risk by the operation.

DR. SWAIN: Any other questions -- and I don't know that we have really helped the FDA with this second part about future developments, what are the best methods of assessing the effectiveness of TMR because I think we are all aware that there is probably somebody else that wants to have a device approved. Have we discussed enough, Tom?

DR. CALLAHAN: Well, I think you have certainly given us some insight into some of the things that you are thinking about. We could probably discuss it for another week and try to -- but I think those points are worthwhile and we will certainly consider those.

Now I think that is probably adequate.

DR. VETROVEC: Can I just add one thing. I think Ward -- Dr. Casscells has made the point about exercise and I would come back to that. I think even if these people were too sick up front to exercise, but if you had late exercise data that showed good functional performance, I

think all of us would be very convinced that that was an important endpoint.

DR. SWAIN: Dr. Weintraub.

DR. WEINTRAUB: For the future -- I am making an assumption that this device will eventually be approved. Sometimes these things do not come back to panel. I would hope that this will eventually and not because I think we need to rubber stamp or approve it, but I am particularly concerned -- and this did not come up in the discussion -- about a device, which is used by chest surgeons, which does not require cardiopulmonary bypass. I think that we really will need to be very careful about where this can be used and under what conditions. And I think that ought to come up for discussion eventually.

DR. SWAIN: Very good point.

Dr. Tracy.

DR. TRACY: Just one last comment and perhaps on the hope that this thing does come back and does eventually get approved, I would just remind everybody that fleckinide(?) can suppress PBCs and make you feel better, but it can kill you. I just want to see that there is long

term mortality information brought out on this.

DR. SWAIN: One possibility of addressing that is a postmarket surveillance, which is done on virtually every device of this type device.

Any other comments? Dr. Callahan.

DR. CALLAHAN: I would just like to comment since it keeps recurring here again and we don't seem to know quite what to do with the data except to go back and look at it again for crossovers, but can you have some suggestion as to how future studies of this type could be designed to minimize it?

DR. CALIFF: I just might as well say what I think. You know, we do studies in severely symptomatic patients all the time, in heart failure, for example, and you just don't -- when a therapy is experimental, you are doing the study because you don't know if it is safe and effective and the compulsion to offer the therapy tot he control arm, I think, is a huge mistake because you rob and cheat, first of all, of the contract you have made to deal with human experiment to answer the question that is being asked and, secondly all future patients of a clean answer.

So, I think we have to really find an environment in which crossover doesn't occur at such a high rate. Otherwise, it seems to me that you are sunk. And there are many examples in other areas of medicine, where highly symptomatic patients are not crossed over.

I think that argument is buoyed in this case by the fact that we have no evidence that this is saving lives. I think if there was evidence that this was a life-saving procedure, then the willingness to go over the brink earlier would be much greater. But, you know, at best what we have got is an equal mortality and some concerns.

So, I think diligence about not crossing over -- maybe going six months with no crossover and then offering the procedure would be a way to do it.

DR. SWAIN: I also think probably from some of the clinical design people when you are looking at a soft endpoint, like angina, to have, let's say, research nurses, whose jobs depend from the company or the investigators or a nuclear medicine doc is probably not the way to do that and that one needs a consistent high quality way to get quantitative data -- qualitative data.

Dr. Friedman.

DR. FRIEDMAN: That is done in many studies that are unblinded and that have subjective outcomes where you have a separate group of people whose only role is to do the assessment and that can be built into almost any study and needs to be.

DR. SWAIN: Also, the emphasis on core labs and trained -- our nuclear medicine comment about trained personnel and machinery that is certified or checked out with blind dummies, I guess.

DR. CALLAHAN: The other question, which we have sort of talked around a little bit and I think we get a sense as to where you are coming from, but in terms of not this particular company with the data that they are dealing with right now, but knowing that other people come forward and we are forever to design or at least to comment on the design -- we don't design, but comment on the designs of the companies, you want to offer a little more succinct advice for what the primary outcome measures might be?

We talked about is -- angina itself is not really enough, but what -- in profusion studies of less than

satisfactory, is there something else higher on the hierarchy that you could suggest?

DR. SWAIN: Well, the other question is the horse out of the barn in that if you didn't have any devices, you were just starting a study, you could specify it. But --

DR. CALLAHAN: No, that is what I mean because we have other --

DR. SWAIN: The horse is out of the barn, unfortunately, on this one.

DR. CALLAHAN: Well, for this particular company but not for others.

DR. SWAIN: Yes, but if this device gets approved, the others only have to meet those standards.

DR. EDMUNDS: Could we get immunity for this company from applying what we suggest because we don't think that they should start from square zero.

DR. CALLAHAN: Right. And I think we heard that loud and clear. We are not talking now about this company but someone might come in tomorrow --

DR. SWAIN: What endpoints do you recommend?

DR. WEINTRAUB: I think this is sort of tough on

this one because the procedure is designed to relieve angina period. I mean, that -- I don't think there was ever much thought that this would prolong life. I mean, maybe, but I think it was so angina directed that it is hard to get around that as an endpoint. Unfortunately, it is a fuzzy endpoint. Now, I don't know what you can do.

Were you talking in general about devices or about this type of device?

DR. CALLAHAN: No, about this type of study and recognizing it is such a soft endpoint and went looking for some kind of a physiologic or anatomic and that is why the profusion studies were suggested.

DR. CALIFF: I would argue strongly against physiologic and anatomic endpoints. The beauty of angina is that you can assess it every living patient and it can be done without bias. It is fuzzy, but it can be done without bias and that has been shown over and over and over and over again.

So, the problem with physiologic endpoints is no matter how hard you try, you always end up with missing data, 20, 25, 30 percent and you never know what to do with

the data that is missing and, after all, the reason to do procedures on people is so that they live longer or feel better. So, angina is a good measure of whether somebody feels better, I think, bolstered by a functional status evaluation. Actually, the CL(?) angina questionnaire data in here is pretty good, if it was just complete.

All six scales go the right direction and I think that is an excellent tool that can be used if it is just complete.

DR. CERQUERIA: I think for the type of patients due to be evaluating this kind of study, the profusion information is important but I think you need to standardize the collection of the data in terms of the protocol, the quality control of the equipment that is going to be used, really encourage compliance at the sites and for something like this, there are sort of newer techniques where you can do a dual isotope approach, where you can get a resting thallium study, which will be a very good marker of viability, perhaps not as good as PET, but pretty close and then you can do, using these technetium compounds, a gaited study to actually get an ejection fraction so that you

standardize the ejection fraction measurement at the time that you are measuring the profusion, so you get functional and profusion information at the same time. And I think that would help to standardize, again, the function, the profusion and you should quantitate all of this as a means of reproducibility and objective findings.

DR. SWAIN: Dr. Ferguson.

DR. FERGUSON: I was interested to hear Dr. Califf just make the statement he did because I have been troubled all day long by the fact that we have been trying, because we don't have definable, other than the soft angina we talk about as an endpoint, we have been talking all day long about trying to correlate angina with other tests.

Tell me I am wrong, if I am, but all the testing that I know about, the correlation may be there but it is very, very rough. So, asking for a number of scans or whatever other tests, treadmill testing and so forth and trying to correlate that as angina -- what we are really trying to get at when we do that is the reason this works.

You know, we are delving into that problem with these others, are we not? I mean, that is my question.

DR. CALIFF: In general, I think that is true. It is a little more complicated here, I think, because of the concern about the placebo effect, which none of us would want to subject someone to an operative risk if it was purely a placebo effect, but in general, I agree with what you said, that if we show the patient feels better with regard to angina and it is striking, that is what people want. But we also need to know that we haven't harmed them in some other way.

DR. EDMUNDS: But I would support trying to get a second measure of efficacy and that is showing a demonstrated increase in blood flow to the treated area in both the controls and in the study group. In other words, I would like to see if you are going to do one of these more sophisticated thallium studies or, better, a PET scan on a smaller number of patients that you would randomize them rigorously, that you would examine their angina, evaluate their angina rigorously, but that you would also do your imaging targeting, let's say, the anterior apical part of the heart if that is what you are going to laser or the lateral wall, specifically both in controls and in treated

groups because these patients do product collaterals on their own and they might very well -- the controls have increased profusion, too, when you have better resolution of the imaging technique.

But I would vote to try to get as many measures as you can and as many objective measures as you can.

DR. SWAIN: Dr. Ferguson.

DR. FERGUSON: I just want to respond to that. I couldn't agree more, Hank, with what you are saying. My question is if we ask them to get a lot of data and it doesn't correlate with the angina, are we back here with the same problem? That is my question.

DR. VETROVEC: That was one of my reasons for suggesting late exercise testing because that would be less looking at mechanism but more looking at the functional outcome of what you have done. I think we would all agree that not having pain and being able to exercise would be two very good factors that would suggest you had done something worthwhile for a patient.

DR. PARISI: I think if you really can show in as objective a way as you can you have relieved angina, the

profusion studies really just reflect on the mechanism, which is nice to know and particularly useful if it is clear cut, but I think if we can just see exactly what is happening with the angina, I think it would be reasonable. I think you should pursue the other endpoint.

I think the exercise test is a good suggestion. It would give supplementary information.

DR. SWAIN: I would say to the FDA that, you know, we have assembled such a stellar committee here for this evaluation and that I am sure that everybody or if someone isn't willing, to please speak up right now, to be available, you know, telephone consultation for more discussion of this, of what they think and perhaps something more formal even.

We did that on another device. A couple of panel members were extremely helpful. So, I assume that you would be willing to help out the FDA in this very complex problem.

We are going to adjourn in a second. I have to remind the panel members that this is all confidential and this whole device book needs to stay here and for the people coming tomorrow, that you take tomorrow's booklet for that

device back up to your rooms and it not be left here.

We are adjourned.

[Whereupon, at 5:10 p.m., the meeting was concluded.]